CHAPTER 20

Systemic Diseases

Acromegaly

Acromegaly is caused by excessive growth hormone (GH) occurring during adult life, after epiphyseal closure, and is almost invariably due to a secreting pituitary acidophil adenoma. (Hypersecretion of growth hormone in childhood, prior to epiphyseal closure, results in gigantism.)

1. **Presentation** is in the fourth to fifth decades.
2. **Signs**
   a. *Skin*. Hyperhidrosis, seborrhoea, acne and in females hirsutism.
   b. *Face*. Coarseness of features: thick lips, exaggerated nasolabial folds, prominent supraorbital ridges (Fig. 20.1) and enlargement of the lower jaw (prognathism) (Fig. 20.2) with dental malocclusion.
   c. *Enlargement* of the head, hands, feet, tongue (Fig. 20.3) and internal organs.
3. **Complications** include osteoarthritis (Fig. 20.4), carpal tunnel syndrome, cardiomyopathy, hypertension, respiratory disease, diabetes mellitus, gonadal dysfunction and neuropathy.
4. **Diagnostic tests**. The diagnosis may be confirmed by noting GH levels in response to an oral glucose tolerance test. Normal individuals manifest suppression of GH levels to below 2 mU/l. However, in acromegaly, GH levels do not fall, and may paradoxically rise.
5. **Treatment** options include bromocriptine (a long-acting dopamine agonist), radiotherapy (external beam or by implantation of yttrium rods in the pituitary) and trans-sphenoidal hypophysectomy.



Fig. 20.1
Acromegaly



Fig. 20.2
Plain skull radiograph of acromegaly showing an enlarged mandible with widening of the mandibular angle (prognathism), enlarged frontal sinus, thickening of the skull vault and an expanded pituitary fossa (Courtesy of S. Ghiacy)

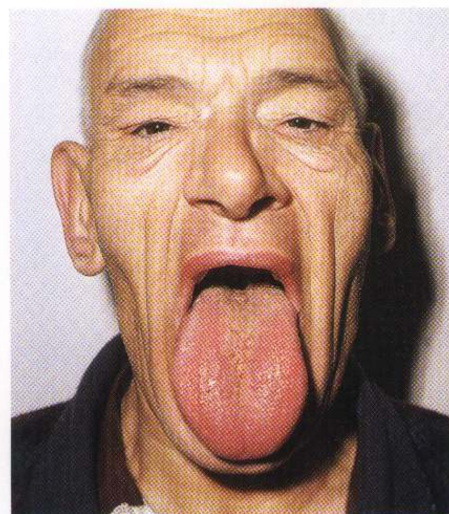


Fig. 20.3
Macroglossia in acromegaly



Fig. 20.4
Plain radiograph of the hands in acromegaly showing lips and hooks of the terminal phalanges, enlarged bones with prominent muscle attachments and early osteoarthritic changes (Courtesy of S. Ghiacy)

6. **Ophthalmic features**
   a. ***Common***. Bitemporal hemianopia and optic atrophy.
   b. ***Rare***. Angioid streaks and see-saw nystagmus of Maddox.

Acquired immunodeficiency syndrome

Acquired immunodeficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV), which is predominantly transmitted by sexual intercourse and occasionally by contaminated blood or needles. On a worldwide basis, heterosexual intercourse is the predominant mode of transmission; in the Western world, however, AIDS is commonly transmitted by homosexual contact. Transmission may also occur transplacentally or via breast milk. Infection with HIV is typically followed by a latent period, after which develop the clinical manifestations of AIDS. HIV targets CD4+T-(helper) lymphocytes, which are vital to the initiation of the immune response to pathogens. A steady decline in the absolute number of CD4+T-lymphocytes therefore occurs, resulting in progressive immune deficiency, particularly that of cell-mediated immunity. Regular estimation of the CD4+T count is therefore a useful measure of disease progression. Apart from immunodeficiency, HIV also has the property of mediating direct damage to the central nervous system.

1. **Presentation**
   a. ***Acute seroconversion illness***. HIV infection is sometimes followed a few weeks later by constitutional symptoms such as fever, headache, malaise and a maculopapular rash, associated with generalized lymphadenopathy, soon after which anti-HIV antibodies appear.
   b. ***An asymptomatic phase***, often lasting many years, then follows, during which steady depletion of CD4+T-lymphocytes occurs.
   c. ***Symptomatic HIV infection*** (AIDS) then follows, characterized by immunosuppression with opportunistic infections and tissue damage directly due to HIV infection.
2. **Opportunistic infections** in AIDS include:
   a. ***Protozoan***. Toxoplasma, cryptosporidium, microsporidium and *Pneumocystis carinii*.
   b. ***Viral***. Cytomegalovirus, herpes simplex and zoster, molluscum contagiosum and Epstein–Barr.
   c. ***Fungal***. Cryptococcus, candida (Fig. 20.5) and histoplasma.
   d. ***Bacterial***. *Mycobacterium tuberculosis, Mycobacterium avium*, staphylococci, streptococci, *Haemophilus* and *Bartonella henselae*.
3. **Tumours** include Kaposi sarcoma (Fig. 20.6), non-Hodgkin B-cell lymphoma and squamous cell carcinoma of the cervix and anus.
4. **Other manifestations** include HIV wasting syndrome, encephalopathy and progressive multifocal leucoencephalopathy.
5. **Diagnostic tests**. Serological testing for HIV infection should be performed only with informed consent after proper counselling, due to the profound implications of a positive result. HIV is confirmed most commonly by the demonstration of anti-HIV antibodies in the serum, by the ELISA and western blot tests. 'Seroconversion' may take 3 months or longer to occur following exposure to the virus, sometimes necessitating serial testing in individuals at high risk. Subsequent to the establishment of HIV positivity, CD4+T-lymphocyte counts are measured every 3 months. A CD4+T-lymphocyte count $< 200/\text{mm}^3$ implies a high risk of HIV-related disease. AIDS is diagnosed when an HIV-positive subject develops one or more of a defined list of indicator diseases (Table 20.1).



Fig. 20.5
Oral candidiasis in AIDS



Fig. 20.6
Kaposi sarcoma in AIDS

6. **Treatment**. Although there is no cure for AIDS, the progression of disease can be slowed by a number of drugs. The aim of treatment is to reduce the plasma viral load. Ideally therapy should be commenced before the development of irreversible damage to the immune system.
   a. ***Indications*** for commencement of anti-HIV therapy include:
      - Symptomatic HIV disease.
      - CD4+T-lymphocyte count $< 300/\text{mm}^3$.
      - Rapidly falling CD4+T-lymphocyte count.
      - Viral load $>10{,}000$/ml of plasma.
   b. ***Drug*** treatment is with 'highly active antiretroviral therapy' (HAART), which involves two nucleoside reverse

Table 20.1 AIDS-defining diagnoses (1993 Classification, Europe)

- Candidiasis of bronchi, trachea, lungs or oesophagus
- Cervical carcinoma, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcus, extrapulmonary
- Cryptosporidiosis, with diarrhoea for >1 month
- Cytomegalovirus disease other than in liver, spleen or lymph nodes
- Encephalopathy, HIV-related
- Herpes simplex ulcers for 1 month or bronchitis, pneumonitis or oesophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, with diarrhoea for >1 month
- Kaposi sarcoma
- Lymphoid interstitial pneumonitis
- *Mycobacterium avium* complex or *M. kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis*
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis carinii* pneumonia
- Pneumonia, recurrent
- Progressive multifocal leucoencephalopathy
- Salmonella (non-typhoid) septicaemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome due to HIV (weight loss >10% baseline with no other identified cause)

transcriptase inhibitors with either a non-nucleoside reverse transcriptase inhibitor or one or two protease inhibitors.

- Nucleoside reverse transcriptase inhibitors include zidovudine, lamivudine and zalcitabine.
- Protease inhibitors include amprenavir, indinavir and nelfinadir.
- Non-nucleoside reverse transcriptase inhibitors include efavirenz and nevirapine.

> ***NB:*** Antiretroviral therapy is continuously evolving and should therefore be left to a trained physician.

7. Ophthalmic features

a. ***Eyelids***. Kaposi sarcoma, multiple molluscum lesions and severe herpes zoster ophthalmicus.

b. ***Orbit***. Cellulitis usually from contiguous sinus infection and B-cell lymphoma.

c. ***Conjunctiva***. Kaposi sarcoma, squamous cell carcinoma and microangiopathy.

d. ***Cornea***. Keratitis due to microsporidium, herpes simplex and herpes zoster.

e. ***Keratoconjunctivitis sicca***.

f. ***Anterior uveitis***.

g. ***HIV retinopathy*** (cotton wool spots).

h. ***Retinitis***. Cytomegalovirus, varicella zoster (progressive outer retinal necrosis) and toxoplasma.

i. ***Choroiditis***. Pneumocystis and cryptococcus.

j. ***B-cell intraocular lymphoma***.

Ankylosing spondylitis

Ankylosing spondylitis (AS) is a spondarthropathy, primarily involving inflammation, calcification and finally ossification of ligaments and capsules of joints, with resultant bony ankylosis of the axial skeleton. It typically affects males, 90% of whom are HLA-B27 positive.

1. Presentation is in early adulthood with insidious onset of pain and stiffness in the lower back or buttocks. This is initially worse after inactivity, but may be aggravated by weight bearing.

2. Signs

a. ***Arthritis***. In order of frequency, the joints most affected are the sacro-iliac, spine, hips, ribs and shoulders.



Fig. 20.7
Limitation of spinal flexion in advanced ankylosing spondylitis



Fig. 20.8
Severe spinal involvement in ankylosing spondylitis with bony bridging by syndesmophytes ('bamboo spine') (Courtesy of S. Ghiacy)

Progressive limitation of spinal movements occurs (Fig. 20.7); the spine characteristically becomes fixed in flexion. Reduced mobility of the thoracic cage may predispose to pulmonary infection.

b. Enthesopathy of the plantar fascia and Achilles tendon.

3. **Associations**. Inflammatory bowel disease (colitic arthritis).
4. **Complications**. Apical pulmonary fibrosis, aortic incompetence and cardiac conduction defects.
5. **Diagnostic tests**. The ESR is raised. Radiology of the sacro-iliac joints reveals juxta-articular osteoporosis in the early stages, later followed by sclerosis and bony obliteration of the joint. The spinal ligaments may also manifest calcification ('bamboo spine') (Fig. 20.8), as may other joints involved by the inflammatory process.
   NB: Radiological changes often pre-date clinical symptoms.
6. **Treatment** options include physiotherapy, NSAIDs, sulphasalazine and intra-articular steroid injections. Surgical correction of bony deformities may be necessary.
7. **Ophthalmic features**. Acute anterior uveitis in 30%.

Atopic eczema

Atopic eczema (dermatitis) is an idiopathic, often familial, skin condition, which may be associated with asthma and hay fever.

1. **Presentation** is with intense pruritus usually in infancy, but may be at any age.
2. **Signs**
   a. Facial eczema is usually seen in infants and consists of itchy, dry, erythematous papules (Fig. 20.9).
   b. Flexural eczema (Fig. 20.10) usually develops later with symmetrical involvement of the elbow and knee flexures, wrists and ankles by dry, lichenified or excoriated skin.
3. **Treatment** options include emollients, coal-tar preparations and topical steroids.
4. **Ophthalmic features**
   a. Common. Madarosis and staphylococcal blepharitis.
   b. Uncommon. Chronic keratoconjunctivitis, keratoconus and early-onset cataract.
   c. Rare. Retinal detachment.

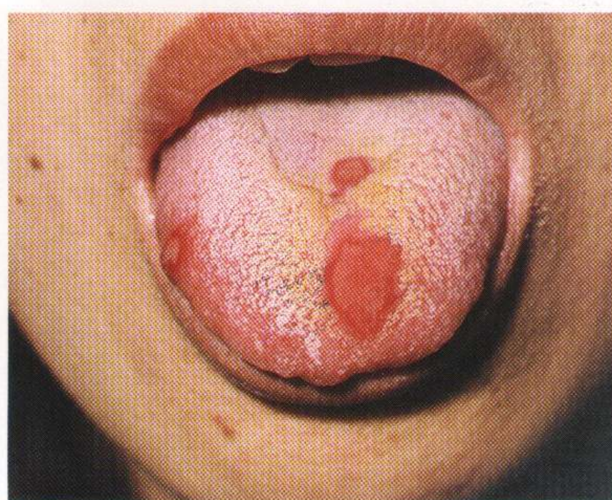

Fig. 20.9
Infantile eczema


Fig. 20.10
Adult eczema

Behçet disease

Behçet disease is an idiopathic, recurrent, multisystem disease. It typically affects young men from the eastern Mediterranean region and Japan and is associated with HLA-B51 and its subtype HLA-Bw51.

1. **Presentation** is in the third to fourth decades with localized lesions such as aphthous ulceration.
2. **Major diagnostic criteria**
   a. Recurrent oral aphthous stomatitis is universal. A typical aphthous ulcer is painful and shallow with a yellowish necrotic base. They occur in crops on the tongue (Fig. 20.11), gums, lips and buccal mucosa.
   b. Skin lesions include erythema nodosum (Fig. 20.12), acneiform (Fig. 20.13), subcutaneous thrombophlebitis, a papulo-vesiculo-pustular rash and hypersensitivity.


Fig. 20.11
Aphthous ulceration in Behçet disease

The latter can be tested with a 'prick' (pathergy) test, in which a pustule appears after puncturing the skin with a needle (Fig. 20.14) or by stroking the skin and demonstrating the appearance of corresponding lines (dermatographism) (Fig. 20.15).



Fig. 20.12
Erythema nodosum-like skin lesions in Behçet disease (Courtesy of B. Noble)



Fig. 20.13
Acneiform skin lesions in Behçet disease (Courtesy of B. Noble)



Fig. 20.14
Pustule formed following pricking in Behçet disease (positive pathergy test) (Courtesy of B. Noble)



Fig. 20.15
Cutaneous hypersensitivity demonstrated by stroking the skin (dermatographism) in Behçet disease (Courtesy of B. Noble)



Fig. 20.16
Genital ulceration in Behçet disease

c. ***Recurrent genital ulceration*** of the penis (Fig. 20.16) and scrotum in males and of the labia and vagina in females.
d. ***Uveitis***, both anterior and posterior.



Fig. 20.17
Dilated superficial veins secondary to deep obliterative thrombophlebitis in Behçet disease. (Courtesy of B. Noble)

3. Minor diagnostic criteria

a. Arthritis involving the knees, ankles and occasionally the sacro-iliac joints.

b. Epididymitis.

c. Intestinal ulceration.

d. Vascular. Obliterative thrombophlebitis of superficial and deep veins (Fig. 20.17), large vessel arterial occlusion and aneurysm formation.

e. Neurological. Brain stem syndromes and meningo-encephalitis.

4. Complete Behçet disease. Four major criteria occurring simultaneously or at different times.

5. Incomplete Behçet disease. One of the following:
- Three major criteria.
- Two major plus two minor criteria.
- Uveitis plus another major criterion.
- Uveitis plus two minor criteria.

6. Treatment

a. Topical tetracycline or steroids for local lesions such as oral or genital ulcers.

b. Systemic therapeutic options include steroids, often in combination with colchicine, azathioprine, cyclosporin, chlorambucil and levamisole.

7. Ophthalmic features

a. Common. Anterior uveitis, vitritis and retinitis.

b. Uncommon. Occlusive retinal periphlebitis, periarteritis and retinal oedema.

Carotid stenosis

Carotid stenosis involves atheromatous narrowing, often associated with ulceration, at the bifurcation of the common carotid artery. The irregularity of the vessel wall may act as a source of cerebral and retinal emboli composed of platelets and fibrin (white emboli) or tiny fragments of atheromatous material (Hollenhorst plaques).

1. Presentation is in the seventh to ninth decades with:
- Transient retinal ischaemic attacks (amaurosis fugax).
- Retinal artery occlusion.
- Transient cerebral ischaemic attacks (TIA).
- Stroke.
- Ocular ischaemic syndrome.
- Asymmetrical diabetic retinopathy—the ipsilateral eye tends to be relatively spared.

2. Signs

a. Palpation of the cervical carotid arteries should be done gently to avoid dislodging a thrombus. Severe or complete stenosis is associated with a diminished or absent carotid pulse. Other peripheral pulses may also be diminished in generalized atherosclerosis.

b. Auscultation over a partial stenosis gives rise to a bruit, best detected with the bell of the stethoscope. It is important to auscultate along the entire length of the artery and to ask the patient to hold his breath. The most ominous bruit is one that is high-pitched and soft because it indicates tight stenosis. When the lumen is narrowed by 90% or more, the bruit disappears.

3. Diagnostic tests

a. Duplex scanning is a non-invasive screening test involving a combination of high-resolution real-time ultrasonography with Doppler flow analysis (Fig. 20.18).

b. Magnetic resonance angiography is non-invasive and accurate (Fig. 20.19).

c. Carotid arteriography is the most accurate method (Fig. 20.20) but carries a significant risk of complications. Resolution can be further improved by digitally removing (subtracting) the distracting background, leaving only the arterial image (Fig. 20.21).

4. Treatment is aimed at preventing stroke and permanent visual impairment by the following:

a. General measures addressing associated risk factors such as smoking, hypertension, diabetes, obesity, hypercholesterolaemia and cardiac arrhythmias.

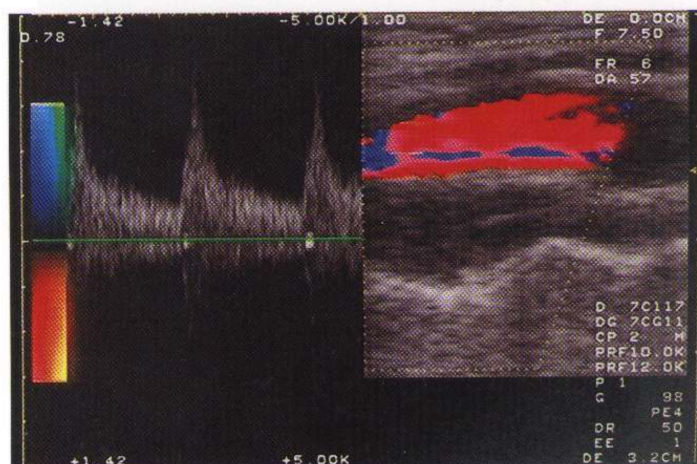
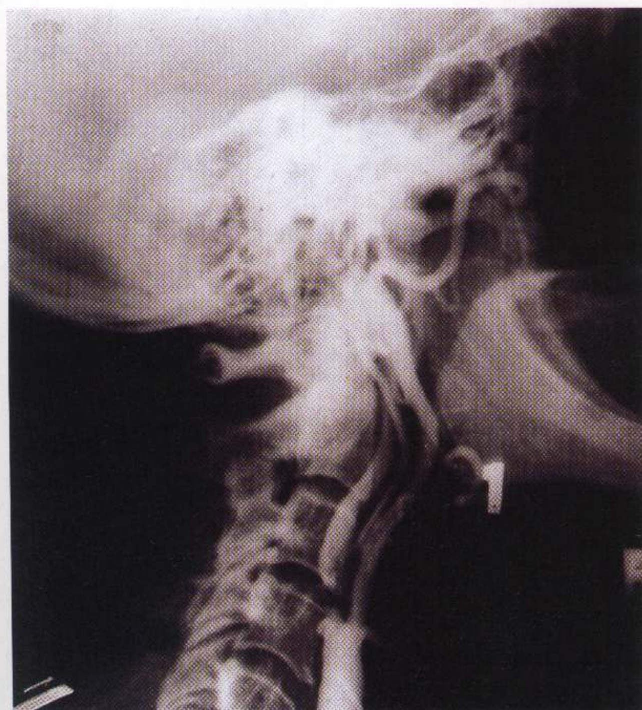


Fig. 20.18
Colour Doppler ultrasonogram showing carotid stenosis


Fig. 20.19
MRA showing severe stenosis of the right internal carotid artery (Courtesy of D. Thomas)


Fig. 20.21
Digital subtraction arteriogram showing severe stenosis of the right internal carotid artery (Courtesy of D. Thomas)


Fig. 20.20
Arteriogram without subtraction showing severe stenosis of the right internal carotid artery (Courtesy of D. Thomas)

*b. **Antiplatelet therapy**.*
- Aspirin 75–300 mg daily.
- Combined aspirin and dipyridamole (Persantin) 200 mg daily, if aspirin alone is ineffective.
- Clopidogrel (Plavix) 75 mg daily if other measures fail.

*c. **Oral anticoagulants*** such as warfarin, if TIAs continue despite antiplatelet therapy.

*d. **Carotid endarterectomy*** (Fig. 20.22) is indicated in patients with symptomatic stenosis greater than 70%.

5. Ophthalmic features

*a. **Common**.* Amaurosis fugax.

*b. **Uncommon**.* Hollenhorst plaques and retinal artery occlusion.

*c. **Rare**.* Hypotensive (slow flow) retinopathy and ocular ischaemic syndrome.

Cat-scratch disease

Cat-scratch disease (fever) is a subacute infection caused by a small Gram-negative bacillus, *Bartonella henselae*, transmitted by a scratch or bite of an infected animal, often a cat.

1. Presentation is at any age with a pustule at the site of inoculation followed by constitutional symptoms, lymphadenopathy and erythema nodosum.



Fig. 20.22
Scar following carotid endarterectomy



Fig. 20.23
Oral involvement in cicatricial pemphigoid

2. **Disseminated disease** is rare but may affect immunocompromised individuals. It is characterized by encephalitis, hepatitis, pneumonia, splenomegaly, splenic abscess formation and osteomyelitis.
3. **Diagnostic tests** include blood cultures and immunofluorescent antibody titres.
4. **Treatment** is with oral doxycycline and rifampicin; the organism is also sensitive to ciprofloxacin and cotrimoxazole.
5. **Ophthalmic features**
   a. Uncommon. Neuroretinitis.
   b. Rare. Parinaud oculoglandular syndrome, intermediate uveitis, acute multifocal retinitis, retinal periphlebitis and exudative retinal detachment.

Chlamydial genital infection

Chlamydial genital infection is sexually transmitted and caused by serotypes D–K of *Chlamydia trachomatis*.

1. **In males** chlamydial infection is the most common cause of 'non-specific urethritis' (NSU) and 'non-gonococcal urethritis' (NGU). It may also cause epididymitis and act as a trigger for Reiter disease.
2. **In females** chlamydia may cause abacterial pyuria, cervicitis, salpingitis, peritonitis and perihepatitis (Fitz-Hugh–Curtis syndrome). Chronic salpingitis may result in infertility.
3. **Treatment**. Doxycycline 100 mg b.d. for 7 days or a single dose of azithromycin 1000 mg.
4. **Ophthalmic features**
   a. Uncommon. Adult conjunctivitis.
   b. Rare. Neonatal conjunctivitis.

Cicatricial pemphigoid

Cicatricial pemphigoid (benign mucous membrane pemphigoid) is a chronic autoimmune (type 2 hypersensitivity) disease characterized by recurrent blisters of the mucous membranes and skin. It affects women twice as often as men and is associated with an increased prevalence of HLA-B12.

1. **Presentation** is in the seventh to eighth decades with ocular or mucocutaneous lesions or both.
2. **Signs**
   a. Mucosal blisters, most frequently oral (Fig. 20.23), rupture within a day or two, leaving erosions and ulcers which heal without scarring. Other sites include the nose, larynx, oesophagus, anus, vagina, glans penis and urethra; ulcers at these sites heal with scarring and may result in stricture formation.
   b. Skin lesions are less common and are of two types.
   - Recurrent, non-scarring blisters which may involve the groins and/or extremities (Fig. 20.24) and may occasionally become generalized.
   - Sparse, localized erythematous plaques associated with recurrent scarring blisters on the scalp and skin near affected mucous membranes.
3. **Treatment**
   a. Local oral lesions may be treated with topical steroids.
   b. Widespread involvement, particularly of the eyes, requires systemic steroids, azathioprine, dapsone or intravenous immunoglobulin.
4. **Ophthalmic features**. Cicatrizing conjunctivitis in the vast majority of cases.

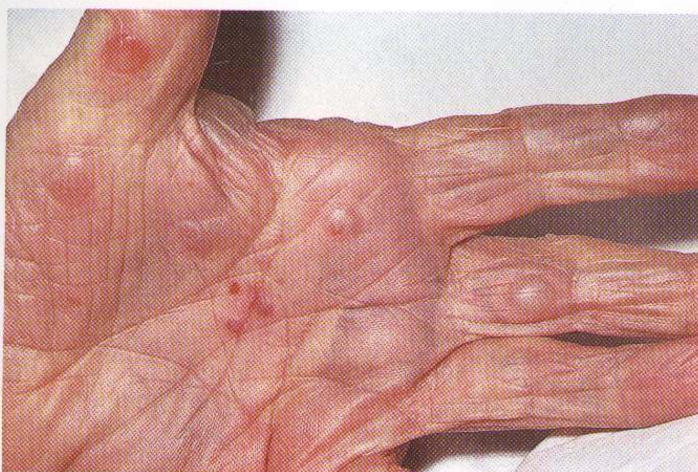


Fig. 20.24
Cutaneous involvement in cicatricial pemphigoid

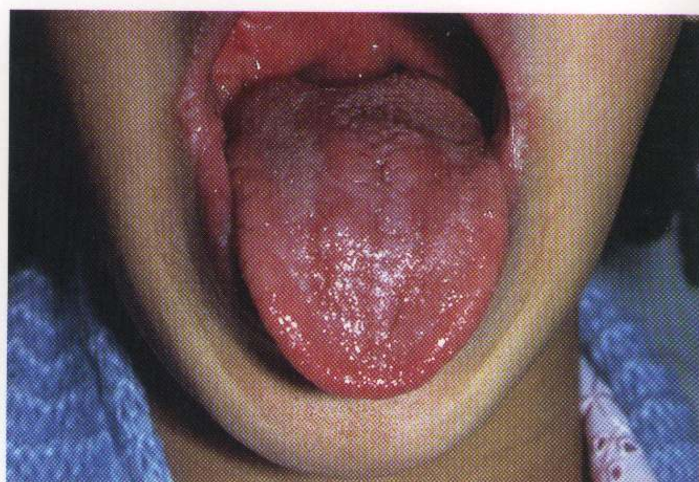


Fig. 20.26
Glossitis in Crohn disease

Crohn disease

Crohn disease (regional ileitis) is an idiopathic, chronic, relapsing disease characterized by multifocal, full-thickness, non-caseating granulomatous inflammation of the intestinal wall. It most frequently involves the ileocaecal region (Fig. 20.25) but any area of the bowel, including the mouth, may be affected.

1. **Presentation** is in the second to third decades with fever, weight loss, diarrhoea and abdominal pain.
2. **Extra-intestinal manifestations**
   a. ***Oral***. Glossitis (Fig. 20.26) and aphthous ulceration.
   b. ***Cutaneous***. Erythema nodosum, pyoderma gangrenosum (Fig. 20.27) and psoriasis.
   c. ***Skeletal***. Finger clubbing, acute peripheral arthritis, sacroiliitis and ankylosing spondylitis.
3. **Complications** include intestinal obstruction due to stricture formation (Fig. 20.28), perirectal fistulae, abscesses and fissures, and liver disease.
4. **Diagnostic tests** include endoscopy and biopsy.



Fig. 20.25
Crohn disease involving the ileocaecal region



Fig. 20.27
Pyoderma gangrenosum in Crohn disease

5. **Treatment** options include nutritional support, steroids, antibiotics, immunosuppressives and surgery.
6. **Ophthalmic features**
   a. ***Uncommon***. Acute anterior uveitis, conjunctivitis, episcleritis and peripheral corneal infiltrates.
   b. ***Rare***. Retinal periphlebitis.

Cushing syndrome

Cushing syndrome is due to prolonged elevation of free plasma glucocorticoid levels.

1. **Causes**
   - Iatrogenic due to systemic administration of steroids (most common).
   - Hypersecretion of glucocorticoids by the adrenal cortex.
   - Hypersecretion of ACTH by a pituitary basophil adenoma (Cushing disease).
2. **Signs**
   a. ***Obesity*** may be generalized or classically involve the trunk, abdomen and neck (buffalo hump).



Fig. 20.28
Barium enema showing stricture and 'rose thorn' ulceration in Crohn disease (Courtesy of S. Ghiacy)



Fig. 20.29
Moon face, hyperpigmentation and hirsutism in Cushing syndrome

b. The face is swollen (moon face) and the complexion plethoric. Females may be hirsute (Fig. 20.29).

c. The skin is thin and susceptible to bruising. Purple striae may be seen (Fig. 20.30). Hyperpigmentation may develop with (ACTH-dependent) Cushing disease.

d. Other features include depression/psychosis, osteoporosis, poor wound healing and proximal myopathy.

3. **Complications** include hypertension, diabetes, pathological fractures and acute necrosis of the femoral head.
4. **Diagnostic tests** are targeted at first establishing the presence of elevated cortisol levels and then identifying the underlying cause (unless iatrogenic); they are best undertaken by an endocrinologist.



Fig. 20.30
Obesity and cutaneous striae in Cushing syndrome

5. **Treatment**
   a. Surgical removal of pituitary adenoma or adrenal secreting tumour. Ectopic foci of ACTH secretion may also be amenable to excision.
   b. Medical suppression of cortisol secretion with metyrapone or aminoglutethimide.
6. **Ophthalmic features**
   a. Common. Steroid-induced cataracts frequently develop in iatrogenic Cushing syndrome but not in Cushing disease.
   b. Uncommon. Bitemporal hemianopia is uncommon with secreting pituitary tumours, which tend to present with systemic features of hypersecretion, as opposed to non-secreting pituitary tumours, which tend to present with chiasmal compression. Glaucoma may develop in susceptible individuals with iatrogenic Cushing syndrome.

Diabetes mellitus

Diabetes mellitus is a common metabolic disorder characterized by sustained hyperglycaemia of varying severity secondary to lack, diminished efficacy, or both of endogenous insulin. The disease affects about 2% of the population in the UK. Despite some degree of overlap, diabetes can be divided into two types:

1. **Type 1** diabetes (insulin-dependent diabetes mellitus, IDDM, juvenile-onset diabetes) develops most frequently between the ages of 10 and 20 years, with acute symptoms of polydipsia, polyuria, nocturia and weight loss. There is an association with HLA-DR3 and -DR4. Autoimmune destruction of pancreatic islet cells is postulated as instrumental in pathogenesis. Type 1 diabetics are often lean and manifest a total lack of insulin; they may develop keto-acidosis and require insulin for glycaemic control.
2. **Type 2** diabetes (non-insulin-dependent diabetes mellitus, NIDDM, maturity-onset diabetes), on the other hand,

develops most frequently between the ages of 50 and 70 years. Type 2 diabetics are often overweight and manifest relative deficiency of insulin and/or peripheral insulin resistance. Metabolic control commonly involves diet and oral anti-diabetic drugs. Some patients may subsequently require insulin for glycaemic control, although many remain non-insulin-dependent. Type 2 diabetes is often initially asymptomatic, and discovered by chance. Alternatively, it may present with recurrent infections of the skin, vulva or glans penis or, rarely, with complications such as vitreous haemorrhage.

3. **Diagnostic tests**
   - A fasting glucose concentration of >6.7 mmol/l.
   - A random glucose concentration of >10.0 mmol/l.
   - A glucose tolerance test is performed only if the diagnosis is uncertain.
   - Glycosylated haemoglobin (HBA1c) reflects the average level of blood glucose over the preceding 6 weeks. Normally 4–8% of haemoglobin is glycosylated; values in excess of this reflect inadequacy of glycaemic control and is a better indicator of the efficacy or otherwise of treatment than a single random glucose level.
   - Urine testing for glycosuria is a crude and unsatisfactory means of monitoring diabetic control.

   NB: Glycosuria per se does not necessarily imply diabetes, as it may merely reflect a lowered renal threshold for glucose excretion.
4. **Treatment**. Type 1 diabetics require insulin; type 2 diabetics require a regimen involving weight reduction, physical exercise and diet control, often in combination with either or both oral hypoglycaemic agents and insulin. Oral anti-diabetic drugs include sulphonylureas (e.g. gliclazide, glipizide) and biguanides (e.g. metformin). It is also important to aggressively treat any associated problems, particularly hypertension and hyperlipidaemia.
5. **Systemic complications**

   a. ***Renal***. Nephropathy is initially characterized by microscopic proteinuria. Severe renal disease may eventually result in renal failure requiring dialysis or transplantation.

   b. ***Vascular***. Accelerated atherosclerosis of coronary and lower limb arteries. Severe involvement of legs may result in ischaemic ulceration and gangrene of the feet and toes (Fig. 20.31).

   c. ***Neurological***
   - Sensory polyneuropathy principally affects the feet in a 'glove and stocking' distribution and may give rise to painless neuropathic perforating ulcers at pressure points in the soles (Fig. 20.32) and degenerative arthropathy (Charcot joints) (Fig. 20.33).
   - Cranial nerve palsies—classically the pupil-sparing third nerve palsy—may occur due to small vessel involvement.

   d. ***Skin*** manifestations include increased susceptibility to bacterial and fungal infections (Fig. 20.34), blistering of the feet and toes, necrobiosis lipoidica (Fig. 20.35) and lipodystrophy at sites of insulin injection (Fig. 20.36) and granuloma annulare.



Fig. 20.31
Diabetic gangrene

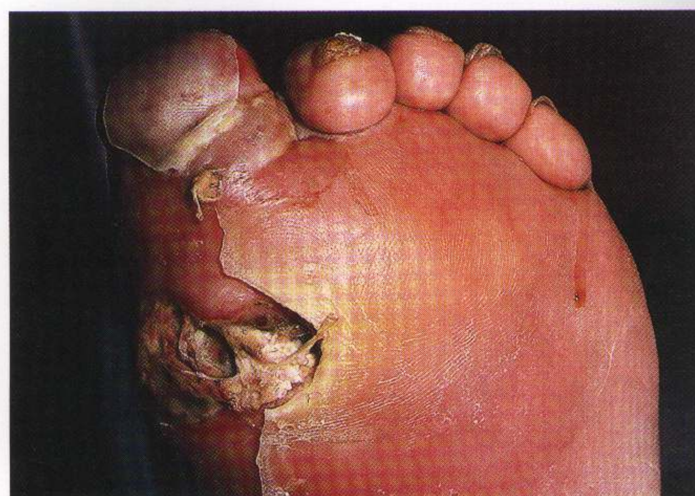


Fig. 20.32
Diabetic neuropathic ulceration



Fig. 20.33
Charcot joints

> ***NB:*** Neuropathy in combination with vascular insufficiency and increased susceptibility to infection commonly results in gangrene of the extremities (diabetic foot).


Fig. 20.34
Moniliasis


Fig. 20.35
Necrobiosis lipoidica


Fig. 20.36
Diabetic lipodystrophy

6. Ophthalmic features

a. Common. Retinopathy and iridopathy (increased iris transillumination).

b. Uncommon. Changes in refraction, accelerated senile cataract, rubeosis iridis, ocular motor nerve palsies and asteroid hyalosis.

c. Rare. Papillopathy, pupillary light-near dissociation, acute-onset cataract and rhino-orbital mucormycosis.

Ehlers–Danlos syndrome type 6 (ocular sclerotic)

Ehlers–Danlos syndrome is a connective tissue disorder involving genetically determined abnormalities of collagen. There are 11 subtypes but only type 6 is associated with ocular features.

1. **Inheritance** is AR.
2. **Signs**
   a. Skin. Thinning, hyperelasticity (Fig. 20.37), bruising and slow healing.
   b. Joints. Hyperextensibility, easy dislocation, repeated falls, hydroarthrosis and pseudo-tumour formation over the knees and elbows.
   c. Vascular. Bleeding diathesis, dissecting aortic aneurysm, spontaneous rupture of large blood vessels and mitral valve prolapse.
3. **Ophthalmic features**
   a. Common. Ocular fragility with increased vulnerability to minimal trauma, blue sclera and microcornea.
   b. Uncommon. Ectopia lentis, keratoconus, cornea plana, high myopia, retinal detachment and angioid streaks.


Fig. 20.37
Cutaneous hyperelasticity in Ehlers–Danlos syndrome

Giant cell arteritis

Giant cell arteritis (GCA) is a granulomatous necrotizing arteritis (Fig. 20.38) with a predilection for large and medium-size arteries, particularly the superficial temporal, ophthalmic, posterior ciliary and proximal vertebral. The severity and extent of involvement are associated with the quantity of elastic tissue in the media and adventitia. Intracranial arteries, which possess little elastic tissue, are usually spared.

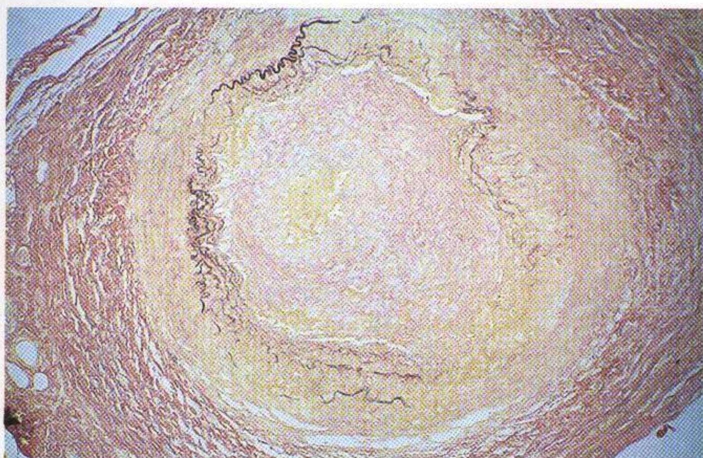


Fig. 20.38
Histology of giant cell arteritis showing granulomatous infiltration, disruption of the internal elastic lamina, proliferation of the intima and complete occlusion of the lumen (Courtesy of A. Garner)



Fig. 20.39
Dilated and tortuous superficial temporal artery in giant cell arteritis



Fig. 20.40
Scalp necrosis in giant cell arteritis

1. **Presentation** is usually in the seventh to eighth decades with the following:
   a. ***Scalp tenderness***, first noticed when combing the hair, is a frequent presenting complaint.
   b. ***Headache***, sometimes severe, may be localized to the frontal, occipital or temporal areas, or more generalized.
   c. ***Jaw claudication*** is virtually pathognomonic. It is caused by ischaemia of the masseter and causes pain on speaking and chewing.
   d. ***Polymyalgia rheumatica*** is characterized by pain and stiffness in proximal muscle groups (typically the shoulders). It is characteristically worse in the morning and after exertion and may precede cranial symptoms by many months.
   e. ***Non-specific symptoms*** such as neck pain, weight loss, fever, night sweats, malaise and depression are common.
   f. ***Blindness*** of sudden onset with minimal systemic upset (occult arteritis) is uncommon.
2. **Other features**
   a. ***Superficial temporal arteritis*** is characterized by thickened, tender, inflamed and nodular arteries (Fig. 20.39), which cannot be flattened against the skull. Pulsation is initially present, but later ceases, a sign strongly suggestive of GCA, since a non-pulsatile superficial temporal artery is highly unusual in a normal individual. In very severe cases, scalp gangrene may ensue (Fig. 20.40).

> ***NB:*** The best location to examine pulsation is directly in front of the pinna.

   b. ***Complications***. Dissecting aneurysms, aortic incompetence, myocardial infarction, renal failure and brain stem stroke.
3. **Diagnostic tests**
   a. ***Erythrocyte sedimentation rate*** (ESR) is often very high, with levels of >60 mm/h. In interpreting the ESR the following should be borne in mind:
      - The normal ESR equals roughly half the age in men; it is 5 mm higher in women.
      - ESR levels of 40 mm/h may be 'normal' in diabetics and in the elderly.
      - Approximately 20% of patients with GCA have a normal ESR.
   b. ***C-reactive protein*** is invariably raised and may be helpful when ESR is equivocal.
   c. ***Temporal artery biopsy*** (TAB) should be performed if GCA is suspected.
      - Steroids should never be withheld pending biopsy, which should ideally be performed within 3 days of commencing steroids.
      - Systemic steroids for more than 7 days may suppress histological evidence of active arteritis; however, this is not invariable and biopsy should still be performed even if steroid therapy has been commenced considerably earlier. This is for two reasons; firstly, if positive it justifies long-term administration of steroids in a population highly prone to their adverse effects. If negative, it provides some justification for tailing off and stopping steroid therapy.

- In patients with ocular involvement it is advisable to take the biopsy from the ipsilateral side. The ideal location is the temple because it avoids damage to a major branch of the auriculotemporal nerve.
- At least 2.5 cm of the artery should be taken and serial sections examined because of the phenomenon of 'skip lesions': segments of histologically normal arterial wall may alternate with segments of granulomatous inflammation.
- Lack of pulsation may render TAB difficult, especially in inexperienced hands; not uncommonly, a segment of nerve is excised and sent for histological examination.

4. **Treatment** involves the administration of systemic steroids (*see* Chapter 18).
5. **Ophthalmic features**
   a. Common. Anterior ischaemic optic neuropathy.
   b. Uncommon. Amaurosis fugax, cotton wool spots, central retinal artery occlusion, cilioretinal artery occlusion and ocular motor nerve palsies (commonly a pupil-sparing third nerve palsy).
   c. Rare. Ocular ischaemic syndrome.

Homocystinuria

Homocystinuria is caused by deficiency of cystathionine-β-synthetase leading to accumulation of homocystine and methionine. The condition is phenotypically similar to Marfan syndrome but carries a thrombotic tendency.

1. **Inheritance** is AR.
2. **Signs**
   - Blond hair with a malar flush (Fig. 20.41).
   - Marfanoid habitus but infrequent arachnodactyly.
   - Mental retardation and psychiatric disturbance.



Fig. 20.41
Blond hair and a malar flush in homocystinuria

3. **Complications**
   - Osteoporosis and spontaneous crush fractures.
   - Thromboses in any vessel and at any age, particularly postoperatively or postpartum.
4. **Treatment** involves oral pyridoxine to reduce homocystine and methionine levels.
5. **Ophthalmic features**
   a. Common. Ectopia lentis.
   b. Uncommon. Myopia and retinal detachment.

Hypertension

Hypertension is most commonly idiopathic (essential) and occasionally secondary to a renal or metabolic disorder.

1. **Presentation** is usually in the fifth to sixth decades.
2. **Signs.** Elevation of blood pressure >140/90 (although the degree of elevation required to diagnose hypertension varies with age).
3. **Complications**
   - Left ventricular hypertrophy and subsequent failure.
   - Increased risk of atherosclerosis resulting in coronary heart disease and stroke.
   - Renal disease.
4. **Treatment** options include lifestyle modification (exercise, weight reduction, diminished salt intake and alcohol consumption) and drug therapy (diuretics, beta-blockers, calcium channel blockers, ACE inhibitors, angiotensin II receptor antagonists and alpha-blockers).
5. **Ophthalmic features**
   a. Common. Retinal arteriolosclerosis and branch retinal vein occlusion.
   b. Uncommon. Retinopathy, retinal artery occlusion, retinal artery macroaneurysm, anterior ischaemic optic neuropathy, choroidal infarcts and ocular motor nerve palsies.
   c. Rare. Exudative retinal detachment (in eclampsia).

Juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) is an inflammatory arthritis of at least 3 months duration developing in children before the age of 16 years. The female:male ratio is 3:2. Patients are seronegative for IgM rheumatoid factor. In North America, however, JIA is frequently referred to as juvenile 'rheumatoid' arthritis.

1. **Presentation.** Based on the onset and the extent of joint involvement during the first 6 months, three types of presentation are recognized:
   a. Pauciarticular-onset JIA accounts for about 60% of cases. It affects girls five times as often as boys, with a peak age of onset of around 2 years. The arthritis involves four or fewer joints, most commonly the knees (Fig. 20.42), although the ankles and wrists may also be affected. Some patients in this subgroup remain pauciarticular, while others subsequently develop a

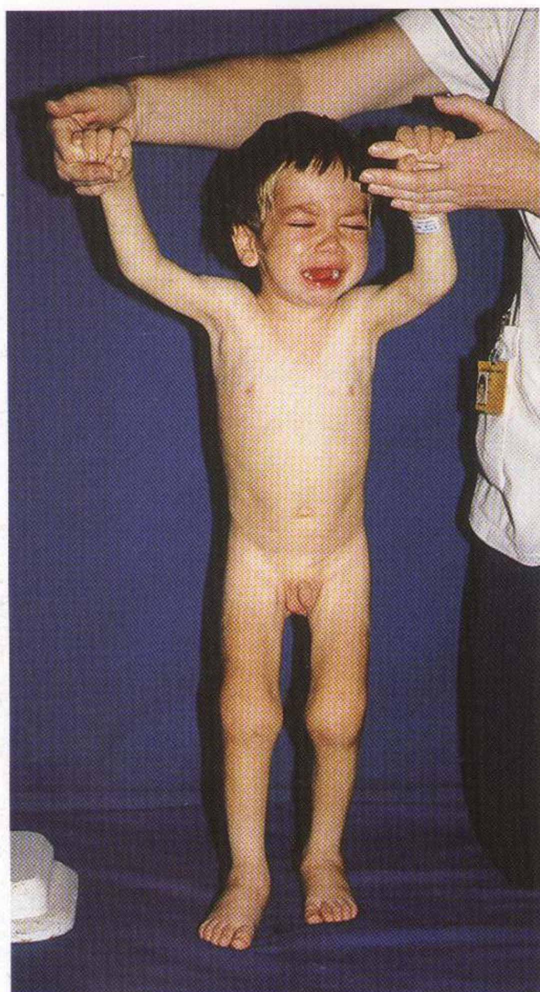


Fig. 20.42
Pauciarticular juvenile idiopathic arthritis involving the knees



Fig. 20.43
Polyarticular juvenile idiopathic arthritis

polyarthritis. About 75% of children are positive for antinuclear antibodies (ANA).

- *Uveitis* is common in this group and affects about 20% of children. Risk factors for uveitis are early-onset of JIA, and positive findings for ANA and HLA-DR5.

b. ***Polyarticular***-onset JIA accounts for a further 20% of cases. It affects girls about three times as often as boys and may commence at any age throughout childhood. The arthritis involves five or more joints, with both small and large joints being involved symmetrically (Fig. 20.43). Systemic features are mild or absent. About 40% of children are positive for ANA.

- *Uveitis* occurs in about 5% of cases.

c. ***Systemic***-onset JIA accounts for about 20% of cases. The disease occurs with equal frequency in boys and girls and may occur at any age throughout childhood. Systemic features include a high remittent fever, transient maculopapular rash, generalized lymphadenopathy, hepatosplenomegaly and serositis. Initially, arthralgia or arthritis may be absent or minimal, and only a minority of patients subsequently develop a progressive polyarthritis. The term '*Still's disease*' is reserved for patients in this subgroup.

- *Uveitis* does not occur.

2. Treatment options include physiotherapy, NSAIDs and low-dose methotrexate.

3. Ophthalmic features. Chronic anterior uveitis.

Kearns–Sayre syndrome

Kearns–Sayre syndrome is a mitochondrial cytopathy associated with mitochondrial DNA deletions.

1. Presentation is in the first to second decades with an insidious onset of bilateral ptosis and limitation of ocular movements in all directions of gaze (progressive external ophthalmoplegia).

2. Signs

- Ataxia and cardiac conduction defects.
- Fatigue and proximal muscle weakness are common.
- Deafness, diabetes, short stature and hypoparathyroidism may be present.

3. **Diagnostic tests**. Lumbar puncture shows increased CSF protein concentration (>1 g/l). ECG demonstrates cardiac conduction defects.
4. **Ophthalmic features**. Symmetrical ptosis, external ophthalmoplegia and pigmentary retinopathy.



Fig. 20.44
Lepromatous cutaneous plaques



Fig. 20.45
Lepromatous cutaneous nodules

Leprosy

Leprosy (Hansen disease, hanseniasis) is a chronic granulomatous infection caused by an intracellular acid-fast bacillus, *Mycobacterium leprae*. The exact mode of infection is unknown although the upper respiratory tract appears the most likely portal of entry.

1. **Lepromatous leprosy** is a generalized, multisystem infection with widespread lesions of skin, peripheral nerves, upper respiratory tract, reticuloendothelial system, eyes, bones and testes. Important signs include:
   a. ***Skin***. Erythema nodosum, plaques (Fig. 20.44) and nodules (Fig. 20.45).



Fig. 20.46
Saddle-shaped nose in leprosy



Fig. 20.47
Shortening of digits in leprosy (Courtesy of T. ffytche)

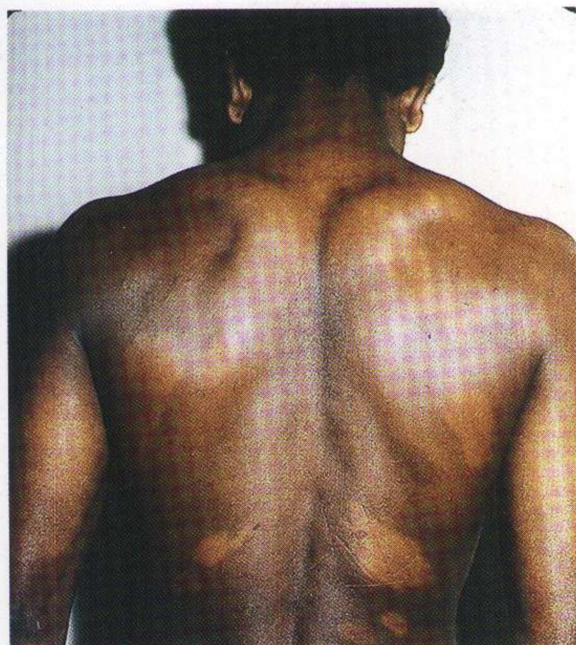


Fig. 20.48
Hypopigmented skin patches in leprosy

b. Nose. Mucosal thickening and saddle-shaped deformity (Fig. 20.46).

c. Neurological. Peripheral neuropathy results in loss of sensory, autonomic and motor function.

- Sensory neuropathy facilitates trauma which may result in shortening of digits (Fig. 20.47) from a multitude of mechanisms.
- Autonomic neuropathy leads to dry, cracked, infection-prone skin; often superimposed on this is secondary bacterial infection, with gross destruction of the tissues.
- Motor neuropathy is exemplified by the 'claw hand' deformity, due to ulnar nerve palsy.

2. **Tuberculoid leprosy** is restricted to the skin and peripheral nerves.

   a. Skin. Annular, anaesthetic, hypopigmented lesions with raised edges (Fig. 20.48).

   b. Nerves. Thickening of cutaneous sensory nerves.

3. **Treatment** is with dapsone, rifampicin and clofazimine.
4. **Ophthalmic features**

   a. Common. Madarosis and lagophthalmos due to seventh nerve palsy. Neurotrophic keratitis due to trigeminal involvement.

   b. Uncommon. Anterior uveitis.

Lyme disease

Lyme disease (borreliosis) is an infection caused by a spirochete, *Borrelia burgdorferi*, transmitted through the bite of a deer tick, *Ixodes ricinus*. Systemic manifestations are complex and are best conceptualized as early and late.

1. **Early** stage presents several days after the bite with a pathognomonic annular expanding skin lesion (erythema chronicum migrans) which may be accompanied by constitutional symptoms and lymphadenopathy. This may last for several weeks and resolve even without treatment. Complications, both neurological (cranial nerve palsies, meningitis) and cardiac (conduction defects, myocarditis), may follow within 3–4 weeks of the initial manifestations.
2. **Late** complications, most commonly chronic arthritis of large joints, may ensue and cause problems for years. Polyneuropathy and chronic acrodermatitis may also occur.
3. **Diagnostic tests** include PCR and ELISA.
4. **Treatment** is with oral doxycycline or intravenous ceftriaxone for neurological involvement.
5. **Ophthalmic features**

   a. Common. Photophobia, pain, periocular oedema and conjunctivitis.

   b. Uncommon. Keratitis, anterior uveitis, intermediate uveitis, optic neuritis, neuroretinitis and ocular motor nerve palsies.

   c. Rare. Peripheral multifocal choroiditis and retinal periphlebitis.

Marfan syndrome

Marfan syndrome is a widespread disorder of connective tissue associated with mutation of the fibrillin gene on chromosome 15q.

1. **Inheritance** is AD with variable expressivity.

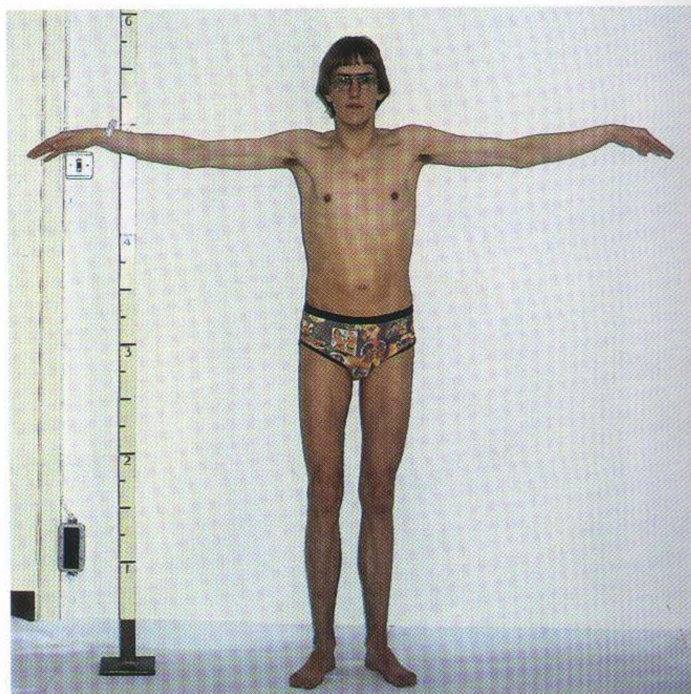


Fig. 20.49
Marfan syndrome (*see text*)

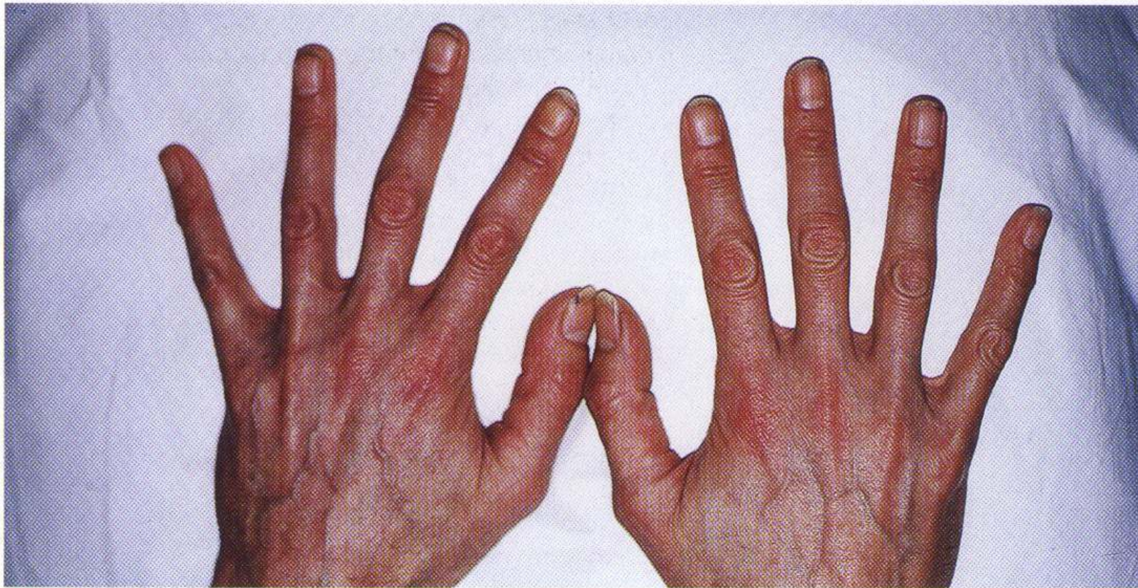


Fig. 20.50
Arachnodactyly in Marfan syndrome

2. Classical signs

a. Musculoskeletal

- Tall, thin stature, scoliosis, sternal deformity (prominence or depression).
- Disproportionately long limbs compared with the trunk (arm span > height) (Fig. 20.49).
- Long spider-like fingers (arachnodactyly) and mild joint hypermobility (Fig. 20.50).
- A narrow and high-arched (gothic) palate (Fig. 20.51).
- Muscular underdevelopment and predisposition to hernias.

b. Cardiovascular

- Dilatation of the ascending aorta leading to aortic incompetence and heart failure (Fig. 20.52).
- Mitral valve disease and aortic dissection.

c. Skin. Striae, fragility and easy bruising.

3. Ophthalmic features

a. Common. Ectopia lentis, hypoplasia of dilator pupillae, angle anomaly, myopia and retinal detachment.

b. Uncommon. Microspherophakia, keratoconus and cornea plana.

c. Rare. Megalocornea.



Fig. 20.51
High-arched palate in Marfan syndrome

Multiple sclerosis

Multiple sclerosis (MS) is an idiopathic, remitting, demyelinating disease involving white matter within the CNS.

1. Presentation is in the third to fourth decades with remitting/relapsing involvement occurring at random frequency and of unpredictable duration.

2. Signs

a. Spinal cord. Weakness, stiffness, sphincter disturbance and sensory loss with a 'trouser-like' distribution.

b. Brain stem. Diplopia, nystagmus, dysarthria and dysphagia.

c. Cerebral hemisphere. Hemiparesis, hemianopia and dysphasia.

d. Psychological. Intellectual decline, depression, euphoria and dementia.

3. Transient features include Lhermitte sign (electrical sensation on neck flexion), dysarthria–dysequilibrium–diplopia syndrome and Uhthoff phenomenon (sudden worsening of vision or other symptoms on exercise or increase in body temperature).

4. Diagnostic tests

a. Lumbar puncture shows leucocytosis, IgG level > 15% of total protein and oligoclonal bands on protein electrophoresis.

b. MRI shows ovoid periventricular and corpus callosum plaques with their long axes perpendicular to the ventricular margins (*see* Figs 18.24 and 18.25). Acute demyelination plaques may be highlighted with gadolinium on T1-weighted scans.

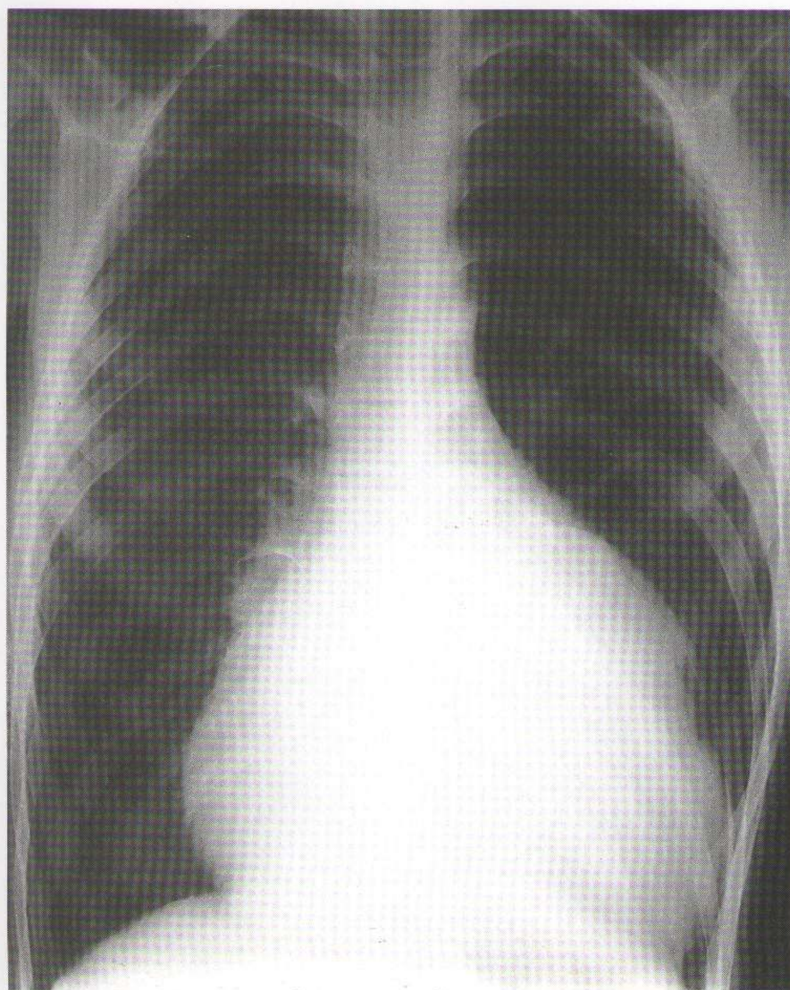


Fig. 20.52
Elongated chest and enlarged heart in Marfan syndrome
(Courtesy of S. Ghiacy)

5. **Treatment** options include systemic steroids and interferon beta-1a.
6. **Ophthalmic features**
   a. *Common*. Optic neuritis (usually retrobulbar), internuclear ophthalmoplegia and nystagmus.
   b. *Uncommon*. Skew deviation, ocular motor nerve palsies and hemianopia.
   c. *Rare*. Intermediate uveitis and retinal periphlebitis.

Myasthenia gravis

Myasthenia gravis is an autoimmune disease in which antibodies mediate damage and destruction of acetylcholine receptors in striated muscle. The resultant impairment of neuromuscular conduction causes weakness and fatiguability of skeletal musculature but not of cardiac and involuntary muscles. The disease affects females twice as commonly as males. Myasthenia may be (a) *ocular*, (b) *bulbar* or (c) *generalized*.

1. **Presentation** is most commonly in the third decade, but may be at any time after the first year of life, most frequently with ptosis or diplopia. Patients with generalized involvement then develop painless fatigue often brought on by exercise, which may be worse towards the end of the day and provoked by infection or stress.
2. **Signs**. The most important feature is fatiguability, affecting musculature of the limbs and that involved in facial expression, ocular movements, mastication and speech.
   a. *Peripheral*. Weakness, particularly of the arms and proximal muscles of the legs. Permanent myopathic wasting may occur in long-standing cases.
   b. *Facial*. Lack of expression (myopathic facies) and ptosis.
   c. *Bulbar*. Difficulties with swallowing (dysphagia), speaking (dysarthria) and chewing.
   d. *Respiratory*. Difficulty with breathing is rare but serious.
3. **Diagnostic tests**
   - Positive edrophonium test (*see* Chapter 18).
   - Raised serum acetylcholine receptor antibody levels.
   - Thoracic CT (Fig. 20.53) or MRI to detect thymoma which is present in 10% of patients. Patients under the age of 40 years without thymoma generally have a hyperplastic thymus; in older patients the thymus is usually normal (atrophic).
4. **Treatment** options include anticholinesterase drugs (pyridostigmine, neostigmine), steroids, immunosuppressive drugs (azathioprine, cyclosporin), plasma exchange, intravenous immunoglobulins and thymectomy. Patients with pure ocular myasthenia are usually not helped by thymectomy.
5. **Ophthalmic features**
   a. *Common*. Ptosis and diplopia. Inability to maintain upgaze. Cogan 'lid-twitch' sign. Weakness of orbicularis oculi with compromised lid closure.
   b. *Uncommon*. Pseudo-internuclear ophthalmoplegia.

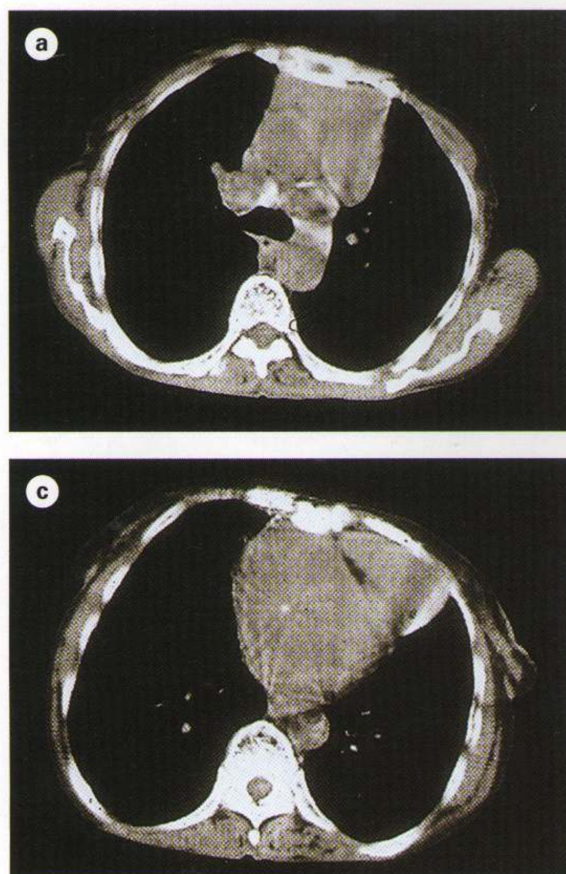
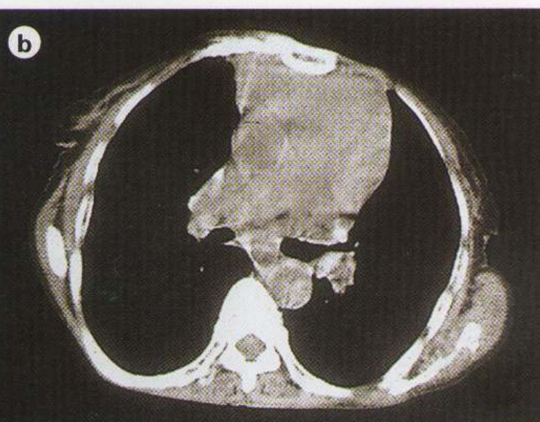



Fig. 20.53
CT scan of the mediastinum showing a thymoma

> *NB:* Bizarre defects of ocular motility may occur; myasthenia should therefore be considered in the differential diagnosis of any ocular motility disorder that does not fit with a recognized pattern.

Myotonic dystrophy

Myotonic dystrophy (dystrophia myotonica, Steinert disease) is characterized by delayed muscular relaxation after cessation of voluntary effort (myotonia). The gene locus is on 19q13.3.

1. **Inheritance** is AD.
2. **Presentation** is in the third to sixth decades with weakness of the hands and difficulty in walking. Successive generations exhibit progressively earlier onset and greater severity of disease, a phenomenon termed 'anticipation'.
3. **Signs**
   a. Peripheral. Difficulty in releasing grip (Fig. 20.54), muscle wasting and weakness.
   b. Central. Mournful facial expression (Fig. 20.55) caused by bilateral facial wasting with hollow cheeks and slurred speech from involvement of the tongue and pharyngeal muscles.
   c. Other. Frontal baldness in males (Fig. 20.56), hypogonadism, mild endocrine abnormalities, cardiomyopathy, pulmonary disease, intellectual deterioration and bone changes.
4. **Diagnostic tests**. Electromyography shows myotonic and myopathic potentials, and serum creatine kinase is elevated.



Fig. 20.54
Difficulty in relaxation of grip in myotonic dystrophy

5. **Treatment** involves exercise and prevention of contractures.
6. **Ophthalmic features**
   a. Common. Early-onset stellate cataracts and ptosis.
   b. Uncommon. External ophthalmoplegia, pupillary light-near dissociation, mild pigmentary retinopathy and low intraocular pressure.

Neurofibromatosis-1

Neurofibromatosis-1 (NF-1, von Recklinghausen disease) is a phacomatosis that primarily affects cell growth of neural tissues. The gene locus is on 17q11.



Fig. 20.55
Mournful facial expression in myotonic dystrophy



Fig. 20.56
Mournful facial expression, frontal balding and right cataract in myotonic dystrophy



Fig. 20.57
Mild macrocephaly in NF-1



Fig. 20.58
Right facial hemiatrophy and fibroma mollusca in NF-1

1. Inheritance is AD with irregular penetrance and variable expressivity.

2. Signs

*a. **Neural tumours*** in the CNS and in cranial, peripheral and sympathetic nerves.

*b. **Skeletal***. Short stature, mild macrocephaly (enlarged head) (Fig. 20.57), facial hemiatrophy (Fig. 20.58), absence of the great wing of the sphenoid bone (*see* Fig. 18.117), scoliosis and thinning of long bone cortex.

*c. **Skin***

- Café-au-lait spots are flat, light-brown patches (Figs 20.59c and 20.60). They appear during the first year of life and increase in size and number throughout childhood; teenagers and adults invariably have more than six.
- Axillary freckles usually become obvious around the age of 10 years and are pathognomonic.
- Fibroma mollusca are pedunculated, flabby nodules (Fig. 20.61) which are often widely distributed over the body (Fig. 20.62 and *see* Fig. 20.59b). They appear at about puberty and increase in number throughout life.

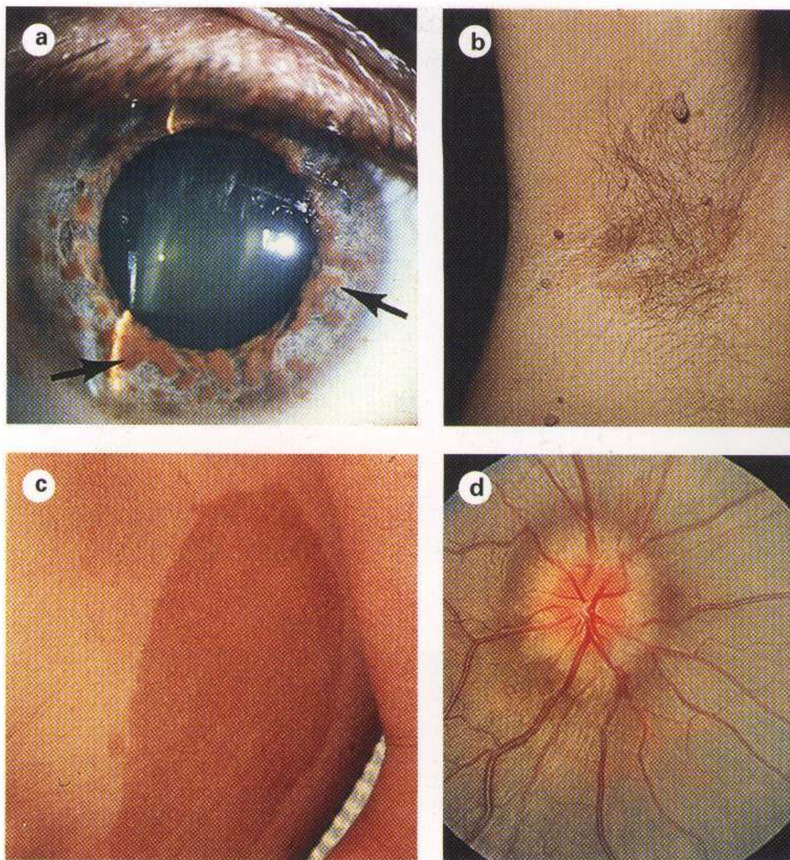


Fig. 20.59
NF-1. (**a**) Lisch nodules; (**b**) fibroma mollusca; (**c**) café-au-lait spot; (**d**) optic disc oedema due to optic nerve glioma (Courtesy of Wilmer Institute)

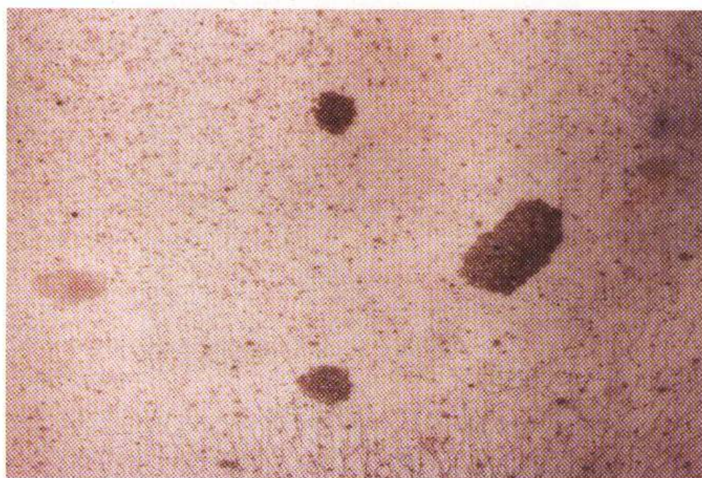


Fig. 20.60
Café-au-lait spots in NF-1



Fig. 20.61
Fibroma mollusca in NF-1

- Plexiform neurofibromas may be associated with pigmentation and overgrowth of the overlying soft tissues (Fig. 20.63 and Fig. 20.64). They may be present at birth or appear during childhood and may occur anywhere on the body. Rarely they may involve the face and cause disfigurement (Fig. 20.65).

3. **Associations** include malignancies, hypertension and mental handicap.
4. **Ophthalmic features**
   a. Common. Eyelid neurofibromas and Lisch nodules (*see* Fig. 20.59a).
   b. Uncommon. Optic nerve glioma (*see* Fig. 20.59d), ectropion uveae and glaucoma.
   c. Rare. Other neural orbital tumours, spheno-orbital encephalocele, prominent corneal nerves, iris mammillations, choroidal naevi, choroidal melanomas and retinal astrocytomas.

Neurofibromatosis-2

Neurofibromatosis-2 (NF-2) is less common than NF-1, with the gene locus at 22q12.



Fig. 20.62
Extensive fibroma mollusca in NF-1

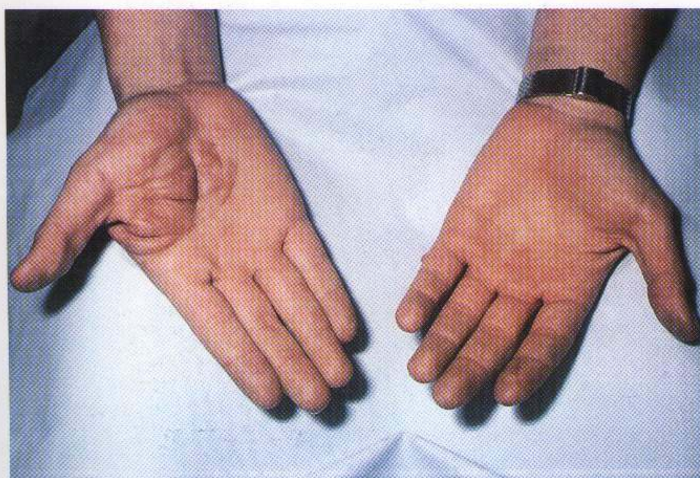


Fig. 20.63
Plexiform fibroma of the right palm in NF-1

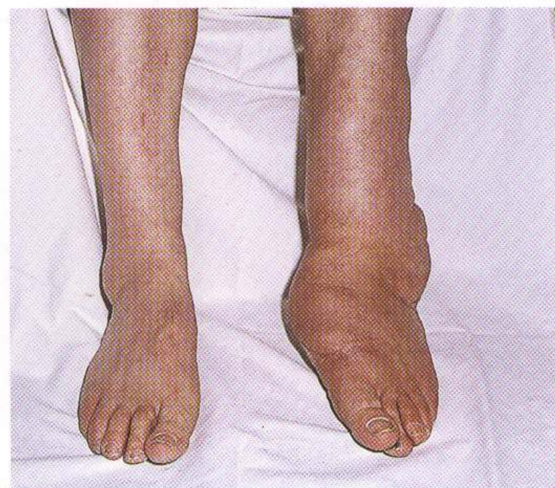


Fig. 20.64
Plexiform neurofibroma and soft tissue hypertrophy in NF-1



Fig. 20.65
Extensive facial plexiform neurofibroma and soft tissue hypertrophy in NF-1

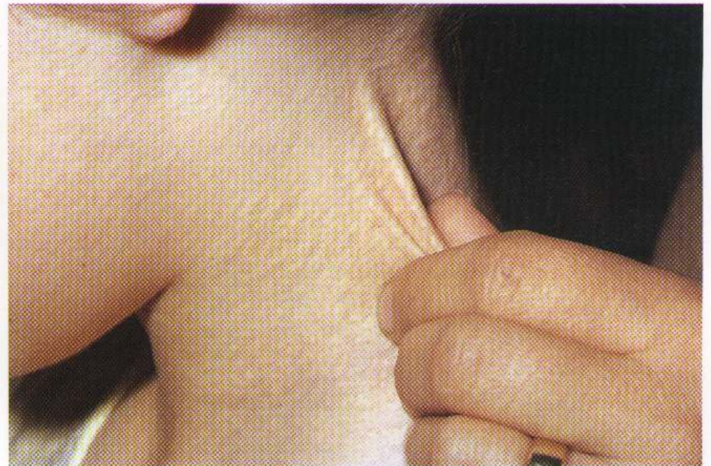
1. **Inheritance** is AD.
2. **Diagnostic criteria**
   a. ***Bilateral acoustic neuromas*** which usually present in the late teens or early twenties with hearing loss, tinnitus or imbalance. Most acoustic neuromas are schwannomas arising from the vestibular nerve. In young patients tumour growth is invariably fast, whereas in older patients the lesion may be either slow- or fast-growing. Recent advances in microsurgical techniques have significantly improved the results of surgery. The gamma-knife (stereotactic radiotherapy) provides a therapeutic option.
   b. ***A patient with a first-degree relative with NF-2*** who also has either a unilateral acoustic neuroma or two of the following: neurofibroma, meningioma, glioma, schwannoma or juvenile cataract.
3. **Ophthalmic features**
   a. *Common*. Early-onset cataract.
   b. *Uncommon*. Ophthalmoplegia, combined hamartomas of the RPE and retina and epiretinal membranes.

Polyarteritis nodosa

Polyarteritis nodosa (PAN) is an idiopathic, potentially lethal, collagen vascular disease affecting medium-sized and small arteries, with frequent aneurysm formation. It is three times more common in males than in females.

1. **Presentation** is in the third to sixth decades with tachycardia, myalgia, arthralgia, fever and weight loss.


Fig. 20.66
Cutaneous vasculitis


Fig. 20.67
Skin papules in pseudoxanthoma elasticum

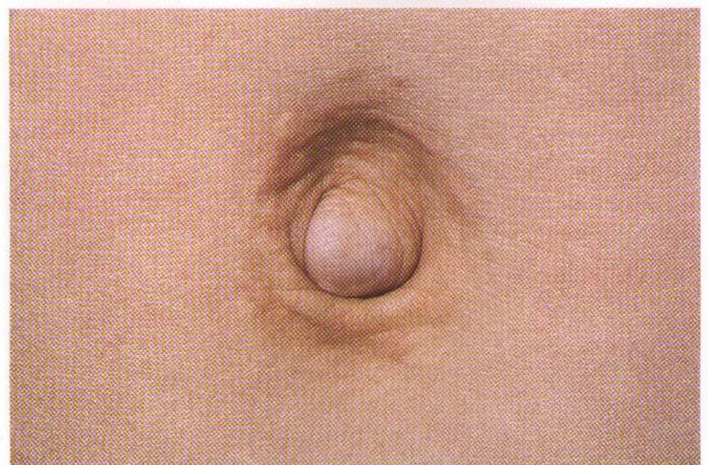
2. **Signs**
   a. ***Skin***. Purpura and easy bruising, vasculitis (Fig. 20.66), infarcts, gangrene and livedo reticularis.
   b. ***Muscles***. Weakness and tenderness.
3. **Complications**
   - Renal involvement and hypertension.
   - Coronary arteritis which may lead to heart failure and myocardial infarction.
   - Gastrointestinal bleeding or an acute abdominal crisis.
   - Stroke or multifocal neuropathy.
4. **Diagnostic tests** show eosinophilia, hypergammaglobulinaemia and necrotizing lesions on skin biopsy.
5. **Treatment** is with systemic steroids and immunosuppressive agents.
6. **Ophthalmic features**
   a. ***Common***. Peripheral ulcerative keratitis and scleritis.
   b. ***Rare***. Orbital pseudo-tumour and occlusive retinal periarteritis.


Fig. 20.68
Loose axillary skin in pseudoxanthoma elasticum

Pseudoxanthoma elasticum

Pseudoxanthoma elasticum is a hereditary disorder of elastin. There are four distinctive types, in which ocular manifestations are common but of variable severity.

1. **Dominant type 1**
   - Small, yellowish skin papules arranged in linear or reticulate plaques most commonly on the neck (Fig. 20.67), axillae (Fig. 20.68), antecubital fossae, groins and paraumbilical area (Fig. 20.69). Involved skin becomes progressively loose.
   - Thin, delicate skin which bruises easily.
   - Accelerated atherosclerosis and mitral valve disease.
   - Severe angioid streaks (Groenblad–Strandberg syndrome).
2. **Dominant type 2**
   - Fewer and flatter skin papules than in dominant type 1.
   - Skin hyperelasticity and high-arched palate.
   - Mild angioid streaks and blue sclera.
3. **Recessive type 1**
   - Skin changes are similar to dominant type 1.


Fig. 20.69
Pseudoxanthoma elasticum involving the paraumbilical area

- Mild vascular disease but frequent gastrointestinal bleeding.
- Mild angioid streaks.

4. Recessive type 2
- Severe and generalized skin changes.
- No systemic complications.
- Angioid streaks.

Psoriatic arthritis

Psoriatic arthritis is a spondarthropathy which develops in about 7% of patients with psoriasis. The disease affects both sexes equally and is associated with an increased prevalence of HLA-B27 and HLA-B17.

1. Presentation is in the third to fourth decades.

2. Signs

a. Skin
- Plaque psoriasis (most common): well-demarcated, salmon-pink areas covered with thick, silvery plaques, commonly seen on extensor surfaces and the scalp (Fig. 20.70).
- Flexural psoriasis: non-scaly pink lesions, commonly affecting the groin and perineum.
- Pustular psoriasis is characterized by pustular lesions on the palms and soles in association with scaling and erythema.
- Erythrodermic psoriasis is characterized by severe erythema and scaling, often with pustule formation, involving the trunk and limbs.

b. Arthritis may take one of the following patterns:
- Asymmetrical involvement of the distal interphalangeal joints which may give rise to sausage-shaped deformities (Fig. 20.71).
- Pauciarticular peripheral involvement.
- Symmetrical peripheral involvement similar to rheumatoid arthritis.
- Arthritis mutilans affecting a few digits is rare.
- Associated ankylosing spondylitis.

c. Nail dystrophy. Pitting, transverse depression and onycholysis (Fig. 20.72).



Fig. 20.70



Fig. 20.71
Sausage-like deformities of digits in psoriatic arthritis



Fig. 20.72
Psoriatic nail dystrophy

3. Treatment. NSAIDs, intra-articular steroids; severe disease may require cytotoxic drugs.

4. Ophthalmic features

a. Uncommon. Acute anterior uveitis.

b. Rare. Conjunctivitis, keratitis and keratoconjunctivitis sicca.

Reiter syndrome

Reiter syndrome (reactive arthritis) is a spondarthropathy which typically affects young males and is characterized by the triad of urethritis, conjunctivitis and arthritis. About 70% of patients are positive for HLA-B27.

1. Presentation is in the third to fourth decades with urethritis, conjunctivitis and arthritis, occurring within a short period of each other, classically following dysentery or sexual intercourse. Presentation may, however, be insidious.

2. Signs

a. Arthritis. Asymmetrical involvement of the knees or ankles is most common and may be migratory. The shoulders, wrists, elbows, hips, spine and sacro-iliac



Fig. 20.73
Achilles tenosynovitis in Reiter syndrome



Fig. 20.75
Circinate balanitis and urethral discharge in Reiter syndrome



Fig. 20.74
Keratoderma blenorrhagica in Reiter syndrome

*b. **Enthesopathy***. Plantar fasciitis, Achilles tendonitis (Fig. 20.73), bursitis and calcaneal periostitis. Reactive bone formation in the latter may result in a calcaneal spur.

*c. **Mucocutaneous***. Painless mouth ulceration, keratoderma blenorrhagica involving the palms and soles (Fig. 20.74), circinate balanitis (Fig. 20.75) and nail dystrophy.

*d. **Genitourinary***. Cystitis, cervicitis, prostatitis, epididymitis and orchitis.

*e. **Aortic incompetence*** is uncommon.

3. **Treatment** is with NSAIDs.
4. **Ophthalmic features**

*a. **Common***. Conjunctivitis and acute anterior uveitis.

*b. **Uncommon***. Corneal infiltrates.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune systemic disease characterized by a symmetrical, destructive, deforming, inflammatory polyarthropathy, in association with a spectrum of extra-articular manifestations and circulating antiglobulin antibodies, termed rheumatoid factors. It affects females more commonly than males.

1. **Presentation** is in the fourth decade and occasionally in childhood (juvenile rheumatoid arthritis). The disease is characterized by exacerbations alternating with phases of quiescence.
2. **Signs**

a. Arthritis

- Symmetrical involvement of the small joints of the hands and feet. Inflammation typically involves the proximal interphalangeal and spares the distal interphalangeal joints. The metacarpophalangeal and wrist joints are also commonly involved.
- Less frequent involvement of the shoulders, elbows, hips and cervical spine.
- Joint instability secondary to chronic inflammation may result in subluxation and deformities, such as ulnar deviation of the metacarpophalangeal joints (Fig. 20.76).

*b. **Skin***. Raynaud phenomenon, vasculitis (Fig. 20.77), subcutaneous nodules (Fig. 20.78) and occasionally pyoderma gangrenosum.



Fig. 20.76
Ulnar deformity of the right hand in rheumatoid arthritis



Fig. 20.77
Cutaneous vasculitis in rheumatoid arthritis



Fig. 20.78
Rheumatoid nodules

3. Complications
- Pulmonary nodules and fibrosis.
- Multifocal neuropathy.
- Septic arthritis.
- Secondary amyloidosis.
- Carpal tunnel syndrome.

4. Treatment options include NSAIDs, gold salts, D-penicillamine, hydroxychloroquine, sulphasalazine, steroids and cytotoxic agents.

5. Ophthalmic features
   a. Common. Keratoconjunctivitis sicca (secondary Sjögren syndrome).
   b. Uncommon. Scleritis and peripheral ulcerative keratitis.
   c. Rare. Acquired superior oblique tendon sheath syndrome.

Rosacea

Rosacea is an idiopathic skin disease which principally affects the glabella, cheeks, nose and chin.

1. Presentation is in adult life with itching and flushing of facial skin, often precipitated by alcohol or spicy food.

2. Signs
- *Stage 1*. Erythema progressing to telangiectasia (Fig. 20.79).



Fig. 20.79
Acne rosacea—stage 1 (*see text*)



Fig. 20.80
Severe acne rosacea—stage 2 (*see text*)

- *Stage 2*. Papules and pustules (Fig. 20.80).
- *Stage 3*. Inflammatory nodules, sebaceous gland hyperplasia (Fig. 20.81) and rhinophyma.

3. Treatment is with topical metronidazole gel and systemic tetracycline.

4. Ophthalmic features
   a. Common. Chronic posterior blepharitis and recurrent meibomian cysts.
   b. Uncommon. Conjunctivitis and peripheral keratitis.

Sarcoidosis

Sarcoidosis is an idiopathic multi-system granulomatous inflammatory disorder, more common in patients of African descent than in Caucasians.

1. Presentation
   a. Acute-onset sarcoidosis typically occurs during the third decade:
   - Löfgren syndrome is characterized by fever, erythema nodosum (Fig. 20.82), bilateral hilar lymphadenopathy (Fig. 20.83) and frequently arthralgia.


Fig. 20.81
Acne rosacea—stage 3 (*see text*)

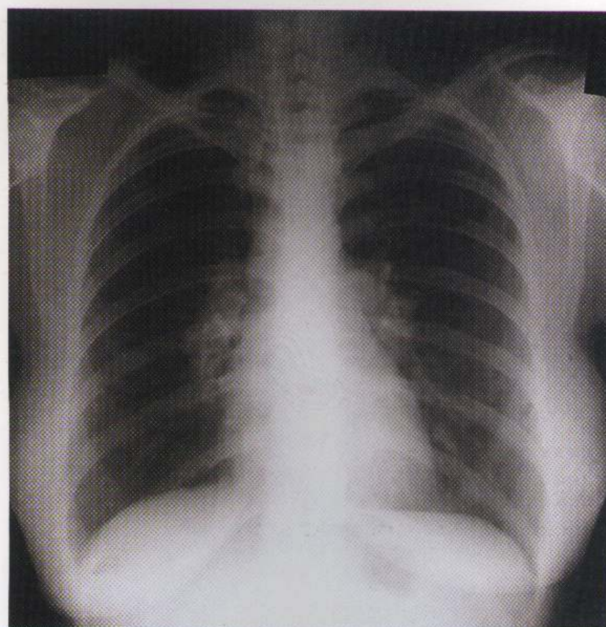

Fig. 20.83
Bilateral hilar lymphadenopathy in acute sarcoidosis


Fig. 20.82
Erythema nodosum


Fig. 20.84
Facial palsy and lupus pernio involving the nose in sarcoidosis

- Heerfordt syndrome (uveoparotid fever) is characterized by fever, parotid gland enlargement and uveitis.
- Seventh nerve palsy (Fig. 20.84) may be associated with other neurological features.

b. ***Insidious-onset*** sarcoidosis typically occurs during the fifth decade with fatigue, dyspnoea and arthralgia.

2. Signs

a. ***Pulmonary*** involvement is present in 90% of patients and varies in severity from asymptomatic bilateral hilar lymphadenopathy to progressive pulmonary fibrosis and bronchiectasis.

b. ***Skin***. Erythema nodosum, granulomata (Fig. 20.85) and lupus pernio (Fig. 20.86). The latter is characterized by indurated, purple-blue lesions.

c. ***Neurological***. Cranial nerve palsies (particularly facial), meningeal infiltration, and intracranial and intraspinal granulomas.

d. ***Other***. Reticuloendothelial, hepatic, renal, bone and cardiac involvement.

3. Diagnostic tests

a. ***Chest radiographs*** are abnormal in 90% of cases.

b. ***Biopsy***

- Of the lungs gives the greatest yield (90%).
- Of the conjunctiva is positive in about 70% of patients.
- Of lacrimal glands is positive in 25% of unenlarged and 75% of enlarged glands.


Fig. 20.85
Cutaneous sarcoid granulomas


Fig. 20.86
Lupus pernio

c. Serum angiotensin-converting enzyme (ACE) is elevated in patients with active disease but normal during remissions. The normal serum level in adults is 32.1 ± 8.5 IU. In patients with suspected neurosarcoid ACE can be measured in the cerebrospinal fluid. ACE may also be elevated in other conditions such as tuberculosis, lymphoma and asbestosis.

d. Bronchioalveolar lavage shows a raised proportion of activated T-helper lymphocytes.

e. Calcium assay may be useful because calcium metabolism is abnormal. Hypercalciuria is common but hypercalcaemia is unusual.

f. Gallium-67 scanning of the head, neck and thorax frequently shows increased uptake.

g. Pulmonary function tests reveal a restrictive lung defect with reduced total lung capacity.

4. **Treatment** options include NSAIDs, steroids and low-dose cytotoxic agents.
5. **Ophthalmic features**
   a. Common. Conjunctival granulomas, anterior uveitis, posterior uveitis and retinal periphlebitis.
   b. Uncommon. Keratoconjunctivitis sicca and intermediate uveitis.
   c. Rare. Fundus granulomas, retinal and disc neovascularization, and papilloedema.

Sjögren syndrome

Sjögren syndrome is characterized by autoimmune inflammation and destruction of lacrimal and salivary glands. The condition is classified as primary when it exists in isolation, and secondary when associated with other diseases such as rheumatoid arthritis and systemic lupus erythematosus. Primary Sjögren syndrome affects females more commonly than males.

1. **Presentation** is in adult life with grittiness of the eyes and dryness of the mouth.
2. **Signs**
   - Enlargement of the salivary glands with diminished salivary flow rate and a dry fissured tongue (Fig. 20.87).
   - Dry nasal passages, diminished vaginal secretions and dyspareunia.
   - Raynaud phenomenon and cutaneous vasculitis.
3. **Complications**
   - Reflux oesophagitis and gastritis.
   - Malabsorption due to pancreatic failure.
   - Pulmonary disease, renal disease and polyneuropathy.
4. **Diagnostic tests**. Serum autoantibodies, Schirmer test and biopsy of minor salivary glands.
5. **Treatment** options include systemic steroids and cytotoxic agents.
6. **Ophthalmic features**
   a. Common. Keratoconjunctivitis sicca.
   b. Rare. Adie pupil.


Fig. 20.87
Dry fissured tongue in Sjögren syndrome

Stevens–Johnson syndrome

Stevens–Johnson syndrome (erythema multiforme major) is an acute, serious but generally self-limiting mucocutaneous, blistering disease, primarily occurring in healthy young individuals. The most frequent precipitating factors of this severe type III hypersensitivity reaction are certain drugs (e.g. sulphonamides, tetracycline, NSAIDs and penicillin), infections with *Mycoplasma pneumoniae* and herpes simplex, and radiotherapy for malignancy. In over 50% of cases there is no apparent cause. The underlying pathology is a generalized vasculitis secondary to deposition of circulating immune complexes.

1. **Presentation** is in the third to fifth decades with constitutional symptoms followed by mucocutaneous lesions.
2. **Signs**
   a. Mucosa
   - Oral and nasal blisters, which rupture forming erosions, are universal; the lips exhibit haemorrhagic crusting (Fig. 20.88).
   - Genital involvement may occur (Fig. 20.89).

   b. Skin
   - A generalized erythematous papular rash, which evolves into 'target' lesions, consisting of erythematous centres surrounded by pale areas, in turn encircled by erythematous rings (Fig. 20.90).
   - Blisters are usually transient but may be widespread and associated with haemorrhage and necrosis (Fig. 20.91).
   - Healing occurs within 1–4 weeks, sometimes leaving a scar.
3. **Treatment** is with systemic steroids; aciclovir may be used if herpes simplex is suspected as the causative agent.
4. **Ophthalmic features**
   a. Common. Transient membranous conjunctivitis.
   b. Uncommon. Cicatricial conjunctivitis.

Sturge–Weber syndrome

Sturge–Weber syndrome (encephalotrigeminal angiomatosis) is a sporadic phacomatosis.

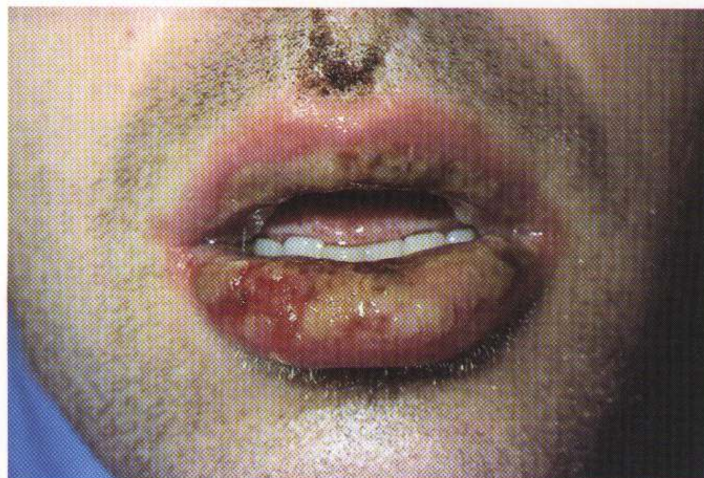


Fig. 20.88
Haemorrhagic crusting in Stevens–Johnson syndrome



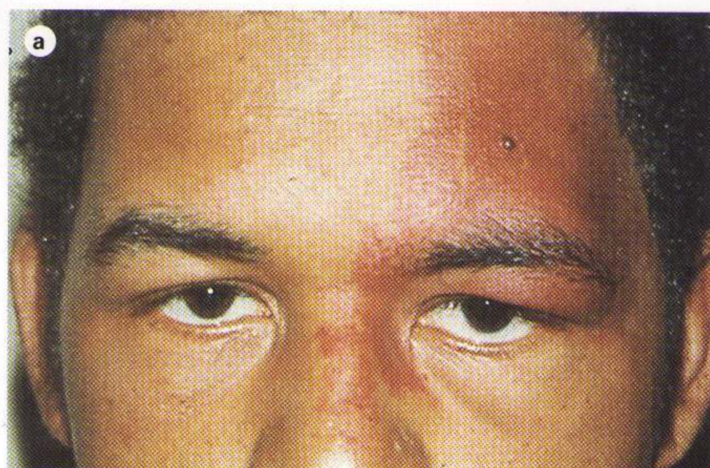
Fig. 20.89
Involvement of the glans penis in Stevens–Johnson syndrome



Fig. 20.90
Target lesion in Stevens–Johnson syndrome



Fig. 20.91
Haemorrhagic vesciculobullous skin lesions and area of necrosis in Stevens–Johnson syndrome



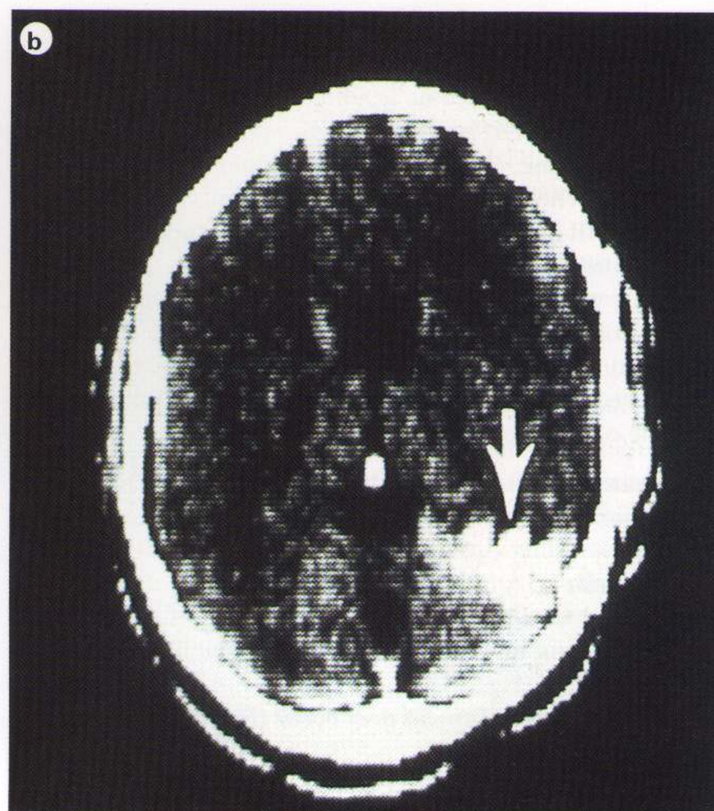


Fig. 20.92
Sturge–Weber syndrome. (**a**) Naevus flammeus; (**b**) axial CT scan showing a meningeal haemangioma (Courtesy of Wilmer Institute)

1. **Classification**
   a. Trisystem involves the face, leptomeninges and eyes.
   b. Bisystem involves the face and eyes or the face and leptomeninges.
2. **Presentation** is at birth.
3. **Signs**
   - Facial naevus flammeus (port-wine stain), extending over an area corresponding to the distribution of one or more branches of the trigeminal nerve (Fig. 20.92a).
   - Ipsilateral parietal or occipital leptomeningeal haemangioma may cause contralateral focal or generalized seizures, hemiparesis and hemianopia.
   - Mental retardation is frequent.
4. **Diagnostic tests**. Plain radiographs may show 'tramline markings' of cerebral calcification. The haemangioma will also be apparent on CT (Fig. 20.92b) and MRI.
5. **Ophthalmic features**
   a. Common. Ipsilateral glaucoma and diffuse choroidal haemangioma.
   b. Uncommon. Ipsilateral episcleral haemangioma.
   c. Rare. Heterochromia iridis.

Syphilis: acquired

Syphilis is a sexually transmitted infection caused by the spirochaete *Treponema pallidum*.

1. **Stages**
   a. Primary stage occurs after an incubation period commonly lasting 2–4 weeks and is characterized by a painless ulcer (chancre) at the site of inoculation (usually genitalia) and associated regional lymphadenopathy.
   b. Secondary stage usually occurs 6–8 weeks after the chancre and is characterized by:
   - Generalized lymphadenopathy with mild or absent constitutional symptoms.



Fig. 20.93
Rash in secondary syphilis



Fig. 20.94
Rash in secondary syphilis

- Symmetrical maculopapular rash on the trunk (Fig. 20.93), palms and soles (Fig. 20.94).
- Condylomata lata in the anal region.
- Mucous patches in the mouth, pharynx and genitalia consisting of painless greyish-white circular erosions ('snail-track ulcers').
- Meningitis, nephritis and hepatitis may occur.
- Secondary syphilis resolves in a few months, even without treatment.

*c. **Latent*** stage follows resolution of secondary syphilis, may last for years and can be detected only by serological tests.

*d. **Tertiary*** stage occurs in about 40% of untreated cases and is characterized by:
- Cardiovascular manifestations: aortitis with aneurysm formation and aortic regurgitation.
- Neurosyphilis: tabes dorsalis, Charcot joints and general paralysis of the insane.
- Gummata in various organs.

2. Diagnostic tests

*a. **VDRL*** (Venereal Disease Research Laboratory). The titres reflect disease activity. It becomes positive during the primary stage and may become negative if treatment is given early.

*b. **FTA-ABS*** (fluorescent treponemal antibody absorption) is specific for treponema antibodies but is not titratable.

*c. **MHA-TP*** (microhaemagglutination assay with *Treponema pallidum* antigen) is specific for treponema antibodies but may be negative in early primary syphilis.

3. Treatment may be with procaine penicillin, doxycycline or erythromycin.

4. Ophthalmic features

*a. **Common***. Madarosis and keratitis.

*b. **Uncommon***. Anterior uveitis, chorioretinitis, periarteritis and neuroretinitis.

*c. **Rare***. Optic neuritis, Argyll Robertson pupils and ocular motor nerve palsies.

Syphilis: congenital

Transplacentally acquired infection may result in stillbirth, stigmata of congenital syphilis or be subclinical.

1. Signs

a. Early
- Rhinitis and failure to thrive.
- Maculopapular rash, especially on the buttocks and thighs, and mucosal ulcers.
- Fissures around the lips, nares and anus.
- Pneumonia, hepatosplenomegaly, lymphadenopathy and jaundice.

b. Late
- Sensorineural deafness.
- Frontal bossing, short maxilla, prognathism, high-arched palate and saddle-shaped nose.
- Malformed incisors (Hutchinson teeth) and mulberry molars.

2. Ophthalmic features

*a. **Common***. Anterior uveitis and interstitial keratitis in early cases.

*b. **Uncommon***. Pigmentary retinopathy in late cases.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune, non-organ-specific connective tissue disease characterized by numerous autoantibodies and circulating immune complexes, which mediate widespread vasculitis and tissue damage. It predominantly affects young females.

1. Presentation is in the third to fifth decades with fatiguability without specific organ involvement. Alternatively, the disease may present with symmetrical arthralgia.

2. Signs

*a. **Mucocutaneous***. 'Butterfly' facial rash (Fig. 20.95), discoid rash (Fig. 20.96), vasculitis, telangiectasia, photosensitivity, alopecia, oral ulceration and Raynaud phenomenon.

*b. **Musculoskeletal***. Arthritis, myositis and tendonitis.

*c. **Renal***. Glomerulonephritis.

*d. **Cardiovascular***. Pericarditis, endocarditis, myocarditis, and arterial and venous occlusions.

*e. **Pulmonary***. Pleurisy, atelectasis and 'shrinking lungs'.

*f. **Haemopoietic***. Anaemia, thrombocytopenia, lymphopenia and leucopenia.

*g. **Reticuloendothelial***. Splenomegaly and lymphadenopathy.

*h. **Neurological***. Polyneuritis, cranial nerve palsies, spinal cord lesions, epilepsy, stroke and psychosis.

3. Diagnostic tests
- The ESR is raised, but C-reactive protein is usually not.



Fig. 20.95
'Butterfly' rash in systemic lupus erythematosus



Fig. 20.96
Discoid lupus

- A variety of autoantibodies including lupus anticoagulant, antiphospholipid and antinuclear may be present.

4. **Treatment** options include antimalarials, NSAIDs, steroids and cytotoxic agents.
5. **Ophthalmic features**
   a. Common. Madarosis and keratoconjunctivitis sicca.
   b. Uncommon. Peripheral ulcerative keratitis.
   c. Rare. Scleritis, retinal vasculitis and optic neuropathy.

Systemic sclerosis

Systemic sclerosis is an idiopathic, chronic, connective tissue disease affecting the skin (scleroderma) and internal organs, occurring most commonly in females under the age of 50. The risk of internal organ involvement is proportional to the extent of skin involvement. Systemic sclerosis may be (a) *limited*, (b) *diffuse*, (c) *sine scleroderma* and (d) *overlap* with other autoimmune diseases.

1. **Presentation** is in the fourth to sixth decades with Raynaud phenomenon.
2. **Signs**
   a. Skin
   - Tightening and thickening on hands, feet, face and trunk (Fig. 20.97) gives rise to a waxy appearance.
   - Subcutaneous fibrosis causes binding-down of skin, tapering of the fingers with loss of pulps (sclerodactyly) (Fig. 20.98) and subcutaneous deposition of calcium (calcinosis).
   - A typical facial appearance characterized by a fixed expression, restrictive movements of the lips and 'beaking' of the nose often develops.

   b. Organs
   - Oesophageal dysmobility.
   - Heart, lung and kidney disease.
   - Mild arthritis and myositis.
3. **Diagnostic tests**. Positive serum antinuclear and other autoantibodies; skin biopsy.
4. **Treatment** is unsatisfactory.
5. **Ophthalmic features**
   a. Common. Eyelid tightening and telangiectasia.
   b. Uncommon. Keratoconjunctivitis sicca.



Fig. 20.97
Scleroderma involving abdominal skin


Fig. 20.98
Sclerodactyly


Fig. 20.99
Goitre in hyperthyroidism

c. Rare. Conjunctival forniceal shortening and vascular changes, nodular episcleritis, scleral pits, retinal cotton wool spots and patches of choroidal non-perfusion seen only on fluorescein angiography.

Thyrotoxicosis

Thyrotoxicosis (hyperthyroidism) is a clinical condition involving excessive secretion of thyroid hormones. Graves disease, the most common subtype of hyperthyroidism, is an autoimmune disorder in which IgG antibodies bind to thyroid-stimulating hormone (TSH) receptors in the thyroid gland and stimulate secretion of thyroid hormones. It is commoner in females and may be associated with other autoimmune disorders.

1. **Presentation** is in the third to fourth decades with weight loss despite good appetite, increased bowel frequency, sweating, heat intolerance, nervousness, irritability, palpitations, weakness and fatigue.
2. **Signs**
   a. External
   - Diffuse thyroid enlargement (Fig. 20.99), fine hand tremor, palmar erythema, and warm and sweaty skin.
   - Finger clubbing (thyroid acropachy) (Fig. 20.100) and onycholysis (Plummer nails).
   - Alopecia, vitiligo (Fig. 20.101) and pretibial myxoedema (Fig. 20.102).
     - Myopathic proximal muscle weakness but brisk tendon reflexes.

   b. Cardiovascular
     - Sinus tachycardia, atrial fibrillation and premature ventricular beats.
     - High-output heart failure.
3. **Diagnostic tests**. Abnormal thyroid function: serum T_3, T_4, TSH, thyroxine-binding globulin (TBG) and thyroid-stimulating immunoglobulin (TSI).
4. **Treatment** options include carbimazole, propylthiouracil, propranolol, radioactive iodine and partial thyroidectomy.


Fig. 20.100
Thyroid acropachy


Fig. 20.101
Vitiligo

5. **Ophthalmic features**
   a. Common. Lid retraction, chemosis and proptosis.
   b. Uncommon. Superior limbic keratoconjunctivitis, keratoconjunctivitis sicca and diplopia.
   c. Rare. Optic neuropathy and choroidal folds.

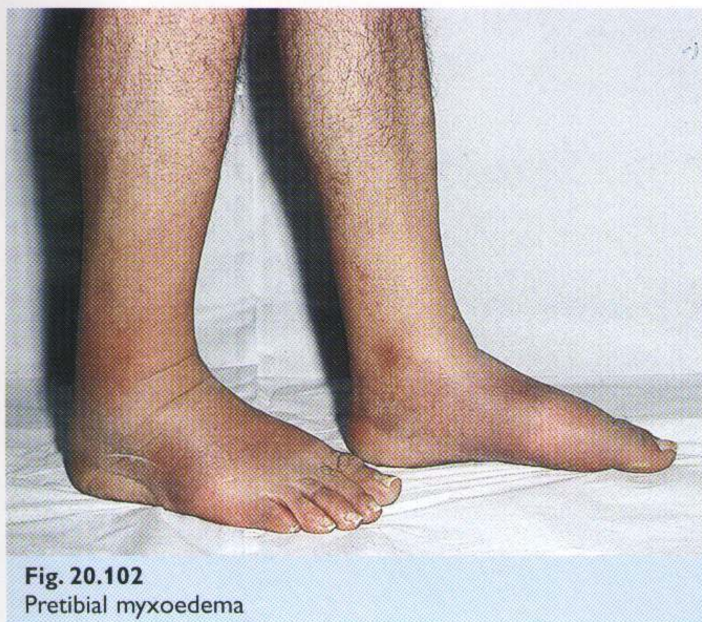


Fig. 20.102
Pretibial myxoedema

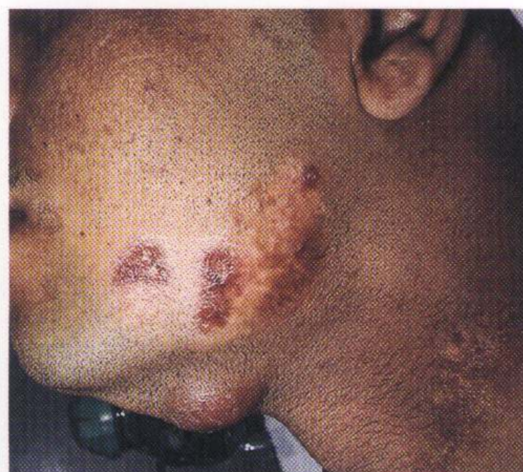


Fig. 20.103
Tuberculosis involving the cervical lymph glands



Fig. 20.104
Tuberculous involvement of the right hip

Tuberculosis

Tuberculosis (TB) is a chronic granulomatous infection caused by the tubercule bacillus, either bovine (*Mycobacterium bovis*) or human (*Mycobacterium tuberculosis*). The former is acquired by drinking milk from infected cattle and the latter by 'droplet infection'. Immunocompromised patients carry an increased risk of TB.

1. **Primary TB** occurs in subjects not previously exposed to the bacillus. It is characterized by the 'primary complex' in the chest (Ghon focus + regional lymphadenopathy), which causes few if any symptoms and usually heals spontaneously.
2. **Post-primary TB** is the result of reinfection or recrudescence of a primary lesion, usually in a patient with impaired immunity. Clinical features include erythema nodosum, fibrocaseous pulmonary lesions and lymph node involvement (Fig. 20.103). Haematogenous spread (miliary TB) may involve many internal organs and bones (Fig. 20.104).
3. **Diagnostic tests**
   a. *Sputum examination* for acid-fast bacilli.
   b. *Chest radiographs*.
   c. *Tuberculin* testing may be useful in the diagnosis of extrathoracic TB. A negative result usually excludes TB, whereas a positive result does not necessarily distinguish between previous exposure and active disease. This is because most individuals have already received Bacille Calmette-Guerin (BCG) and will therefore exhibit a hypersensitivity response.
   d. *Anticord factor antibody* is a new test for ocular TB.
4. **Treatment** is initially with at least three drugs (isoniazid, rifampicin, pyrazinamide or ethambutol) and then with isoniazid and rifampicin.
5. **Ophthalmic features**
   a. *Uncommon*. Granulomatous anterior uveitis, multifocal choroiditis and retinal periphlebitis.
   b. *Rare*. Solitary choroidal granulomas.

Tuberous sclerosis

Tuberous sclerosis (Bourneville disease) is a phacomatosis characterized by the triad of (a) *epilepsy*, (b) *mental retardation* and (c) *adenoma sebaceum*, although not all features are invariably present.

1. **Inheritance** is AD.
2. **Signs**
   a. *Skin*
      - Adenoma sebaceum, consisting of fibroangiomatous red papules with a butterfly distribution around the nose and cheeks, is universal (Fig. 20.105).
      - Ash leaf spots are hypopigmented patches on the trunk (Fig. 22.106), limbs and scalp. In infants with sparse skin pigmentation they are best detected using ultraviolet light, under which they fluoresce (Wood's lamp).



Fig. 20.105
Adenoma sebaceum in tuberous sclerosis



Fig. 20.107
Shagreen patches in tuberous sclerosis



Fig. 20.106
Ash leaf spot in tuberous sclerosis

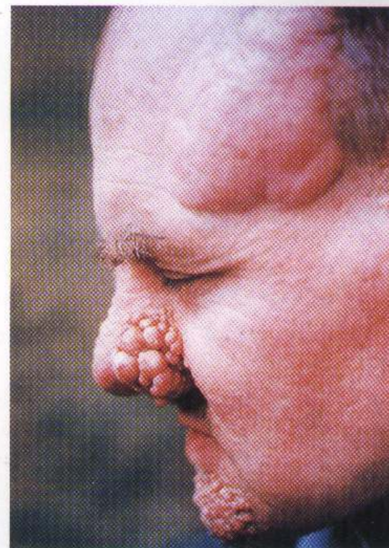


Fig. 20.108
Extensive adenoma sebaceum and a fibrous plaque on the forehead in tuberous sclerosis

- Shagreen patches consist of diffuse thickening over the lumbar region (Fig. 20.107).
- Fibrous plaques on the forehead (Fig. 20.108).
- Skin tags (molluscum fibrosum pendulum).
- Café-au-lait spots.
- Subungual hamartomas (Fig. 20.109).

b. ***Neurological***. Scattered astrocytic cerebral hamartomas are universal (Fig. 20.110).

c. ***Visceral hamartomas***. Renal (angiomyolipomas) and cardiac (rhabdomyomas).

3. Treatment involves control of epilepsy and management of mental and behavioural disorder.

4. Ophthalmic features

a. ***Common***. Retinal astrocytomas in 50%.

b. ***Uncommon***. Hypopigmented spots on the iris and retina, papilloedema and sixth nerve palsy may develop due to raised intracranial pressure.



Fig. 20.109
Subungual hamartoma on the little toe in tuberous sclerosis

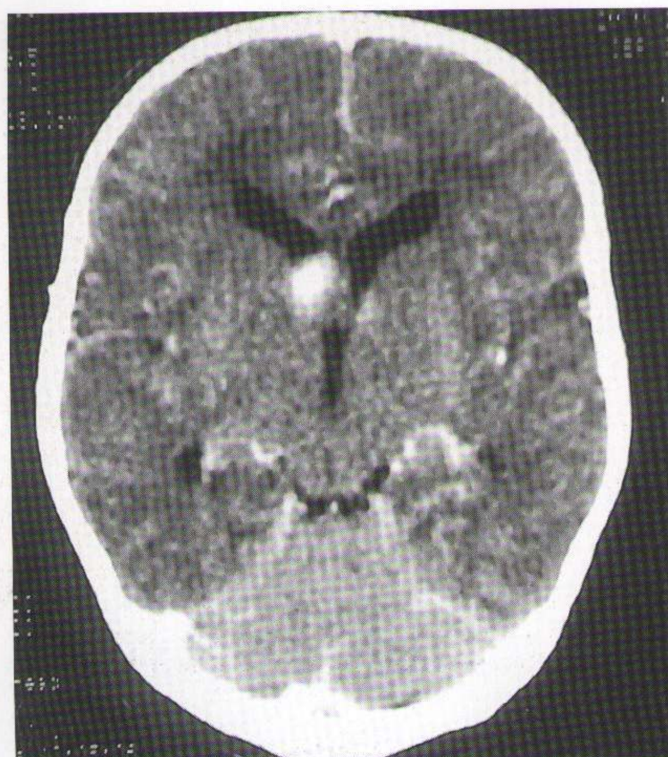


Fig. 20.110
Axial CT scan showing a periventricular astrocytic hamartoma (Courtesy of K. Nischal)

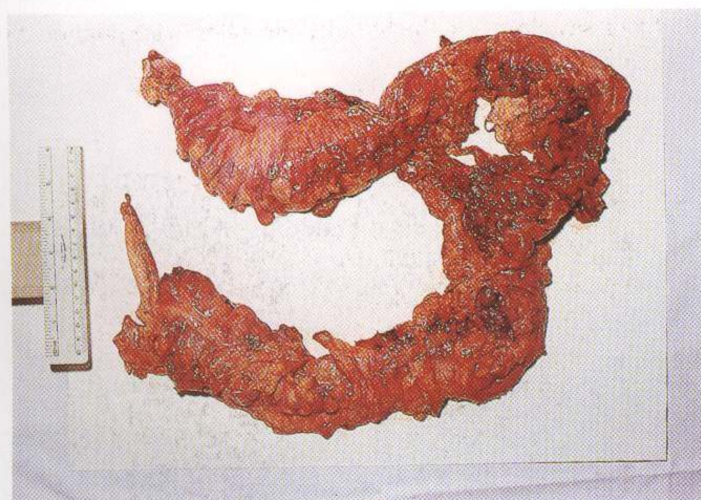


Fig. 20.111
Ulcerative colitis

Ulcerative colitis

Ulcerative colitis is an idiopathic, chronic, relapsing inflammatory disease, involving the rectum and extending proximally to involve part or all of the large intestine. The disease is characterized by diffuse surface ulceration of the mucosa with the development of crypt abscesses and pseudopolyps (Fig. 20.111). Patients with long-standing disease carry an increased risk of developing carcinoma of the colon.

1. **Presentation** is in the second to third decades with bloody diarrhoea, lower abdominal cramps, urgency and tenesmus. Constitutional symptoms include tiredness, weight loss, malaise and fever.
2. **Extra-intestinal signs**
   a. *Mucocutaneous*. Oral aphthous ulceration, erythema nodosum and pyoderma gangrenosum.
   b. *Skeletal*. Finger clubbing, asymmetrical lower limb arthritis, sacroiliitis and ankylosing spondylitis.
   c. *Hepatic*. Autoimmune hepatitis, sclerosing cholangitis and cholangiocarcinoma.
   d. *Vascular*. Arterial and venous thrombosis.
3. **Diagnostic tests**. Endoscopy and biopsy.
4. **Treatment** options include systemic steroids, sulphasalazine, immunosuppressive agents and colectomy.
5. **Ophthalmic features**
   a. *Uncommon*. Acute anterior uveitis, peripheral corneal infiltrates and conjunctivitis.
   b. *Rare*. Papillitis.

Vogt–Koyanagi–Harada syndrome

Vogt–Koyanagi–Harada (V-K-H) syndrome is an idiopathic, multisystem disorder which typically affects Hispanics, Japanese and pigmented individuals. Japanese patients have an increased prevalence of HLA-DR4 and Dw15. In practice, V-K-H can be subdivided into Vogt–Koyanagi disease, characterized mainly by skin changes and anterior uveitis, and Harada disease, in which neurological features and exudative retinal detachments predominate.

1. **Prodromal phase** lasting a few days is characterized by neurological and auditory manifestations.
   a. *Meningitis* causing headache and neck stiffness.
   b. *Encephalopathy* is less frequent and may manifest as convulsions, paresis and cranial nerve palsies.
   c. *Auditory features* include tinnitus, vertigo and deafness.
2. **Acute uveitic phase** follows soon thereafter and is characterized by bilateral granulomatous anterior or multifocal posterior uveitis and exudative retinal detachments.
3. **Convalescent phase** follows several weeks later and is characterized by:
   - Localized alopecia, poliosis and vitiligo (Fig. 20.112).
   - Focal depigmented fundus lesions (sunset glow fundus) and depigmented limbal lesions (Sugiura sign).
4. **Chronic–recurrent phase** is characterized by smouldering anterior uveitis with exacerbations.
5. **Diagnostic criteria** must include at least three of the following:
   - Bilateral chronic anterior uveitis.
   - Posterior uveitis, including exudative retinal detachment, disc swelling and 'sunset glow fundus'.
   - Neurological features.
   - Cutaneous lesions.
6. **Treatment** is with systemic steroids.

von Hippel–Lindau syndrome

von Hippel–Lindau syndrome is a life-threatening phacomatosis.

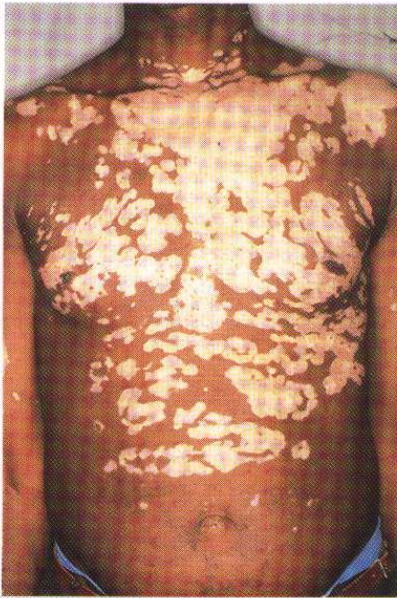


Fig. 20.112
Vitiligo in Vogt–Koyanagi–Harada syndrome

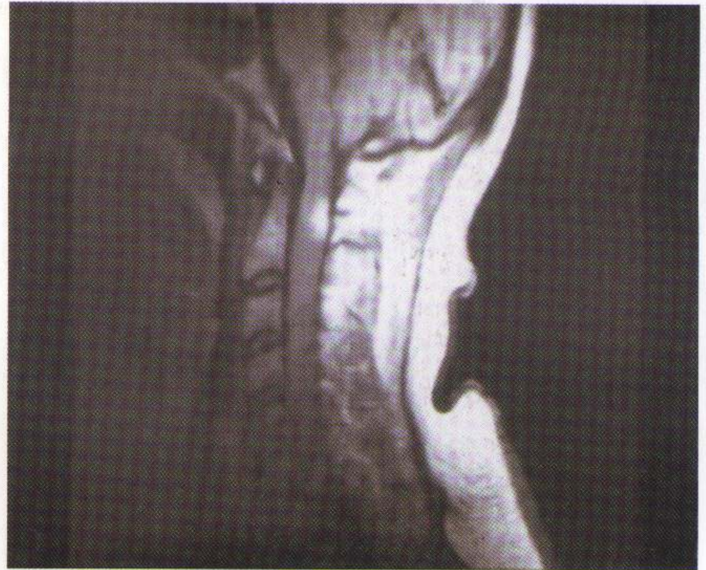


Fig. 20.113
MRI scan showing a haemangioblastoma of the upper cervical cord in von Hippel–Lindau syndrome (Courtesy of D. Thomas)

1. **Inheritance** is AD.
2. **Signs**
   a. Tumours
   - Haemangioblastomas of the cerebellum, spinal cord (Fig. 20.113), medulla or pons.
   - Renal carcinoma (Fig. 20.114) and phaeochromocytoma.

   b. Cysts. Renal, pancreatic, hepatic, epididymal, ovarian and pulmonary.
   c. Polycythaemia.
3. **Ophthalmic features**. Capillary haemangiomas of the retina or optic nerve head.

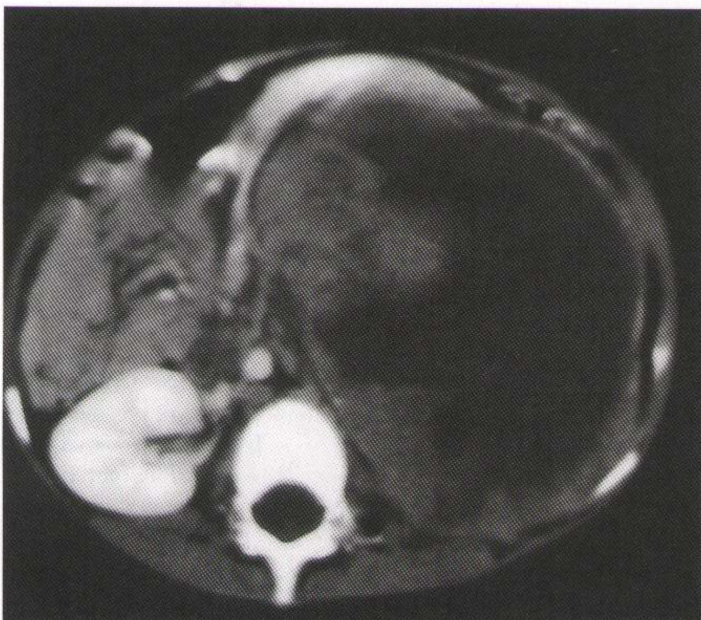


Fig. 20.114
Axial CT scan of the abdomen showing a large renal carcinoma in von Hippel–Lindau syndrome (Courtesy of G. Wilkinson)

Wegener granulomatosis

Wegener granulomatosis is an idiopathic, multisystem, granulomatous disorder characterized by generalized small-vessel vasculitis affecting predominantly the respiratory tract and the kidneys. It affects males more commonly than females.

1. **Presentation** is in the fifth decade, often with pulmonary symptoms.

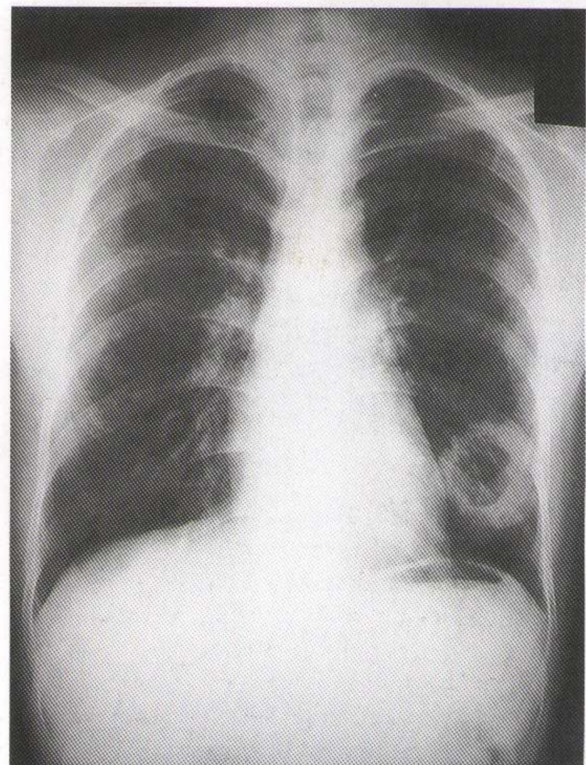


Fig. 20.115
Chest radiograph showing cavitation in Wegener granulomatosis (Courtesy of S. Ghiacy)

2. Signs

a. Respiratory tract

- Upper respiratory tract involvement by necrotizing granulomatous inflammation may result in perforation of the nasal septum, saddle-shaped nasal deformity and nasal–paranasal fistulae.
- Lower respiratory tract involvement may result in nodular lesions, infiltrates and cavitation with fluid levels (Fig. 20.115).

b. Organs

- Necrotizing glomerulonephritis, with renal failure.
- Focal vasculitis involving the spleen, heart and adrenals.

c. Neurological. Polyneuritis and meningoencephalitis.

3. Diagnostic tests. Anti-neutrophil cytoplasm antibodies (c-ANCA) are found in over 90% of patients with active disease.

4. Treatment is with systemic steroids and cyclophosphamide.

5. Ophthalmic features

a. Common. Nasolacrimal obstruction and dacryocystitis.

b. Uncommon. Scleritis and peripheral ulcerative keratitis.

c. Rare. Orbital pseudo-tumour and occlusive retinal periarteritis.